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REVIEW

Reactions of Alicyclic Epoxy Compounds with Oxygen-Centered Nucleophiles

L. I. Kas'yan[1], A. O. Kas'yan[2], and S. I. Okovityi[1]

[1] *Dnepropetrovsk National University, ul. Nauchnaya 13, Dnepropetrovsk, 49625 Ukraine*
e-mail: cf@ff.dsu.dp.ua

[2] *Institut für organische Chemie, Rheinisch–Westfälische technische Hochschule, Aachen, Germany*

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Abstract—The review analyzes the reactions of alicyclic epoxy compounds with oxygen-containing nucleophiles (alcohols, water, and organic acids), describes biologically active products of these reactions, and discusses their mechanisms and results of their simulation by quantum-chemical methods. The regio- and stereoselectivity of nucleophilic reactions of epoxy compounds and the activation of epoxy ring by achiral and chiral catalysts are also considered.

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1. INTRODUCTION

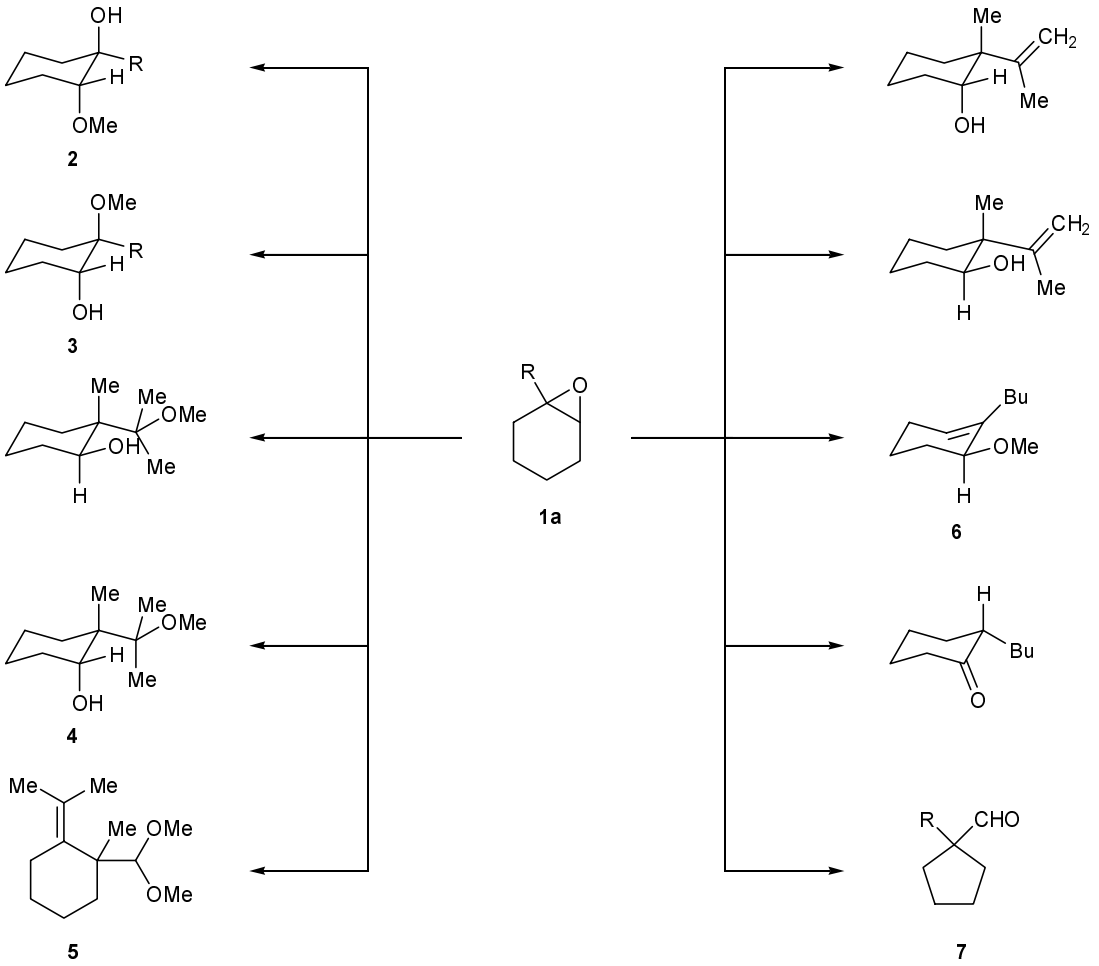
Among reactions of epoxy compounds with nucleophiles, those with alcohols, water, and organic acids were extensively studied, and studies in this line are continuously developing. No special review articles on this topic have been published; however, some reactions of epoxy compounds derived from alicyclic alkenes and epoxy derivatives of methylidenecycloalkanes and substituted norbornenes with the above reagents were discussed in [1–7]. In some cases, isolation of hydrolysis and alcoholysis products of epoxy compounds is unrealistically difficult, for epoxy ring opening in different media gives rise to a diversity of products. As an example, Scheme 1 illustrates possible products of acid-catalyzed methanolysis of 1-*tert*-butyl-1,2-epoxycyclohexane (**1a**) outlined in [8]. The main products are the following: compounds **2**, **4**, and **6** in

Liliya Kas'yan was born in Staryi Oskol (Belgorod Region). In 1960, she graduated from the Odessa State University. Candidate of chemical sciences since 1970, Doctor of chemical sciences since 1990, Honored Scientific and Technical Worker of Ukraine, Professor at the Organic Chemistry Department, Dnepropetrovsk National University. Fields of scientific interest: chemistry of epoxy and cage-like compounds and mechanisms and stereochemistry of organic reactions.

Andrei Kas'yan was born in 1966 in Dnepropetrovsk. In 1988, he graduated from the Dnepropetrovsk State University. Candidate of chemical sciences since 1993. In 1996–2002, A. Kas'yan worked at the Universities of Halle and Aachen (Germany). He is now Head of the chemical laboratory at ProBioGen (Berlin). Field of scientific interest: chemistry of cage-like compounds.

Sergei Okovityi was born in 1970 in Solenoe village (Dnepropetrovsk Region). In 1993, he graduated from the Dnepropetrovsk State University. Candidate of chemical sciences since 1996. Since 2004, he is Head of Organic Chemistry Department, Dnepropetrovsk National University. Fields of scientific interest: quantum-chemical studies on mechanisms of chemical reactions, theoretical methods for calculation of electric and magnetic properties of molecules.

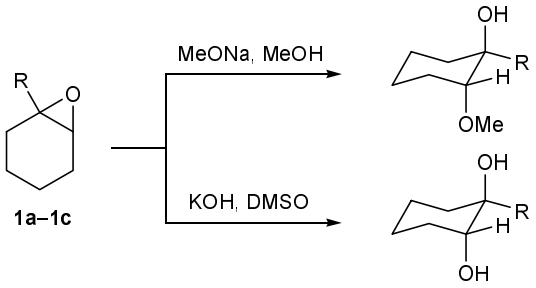
Scheme 1.



R = *t*-Bu.

the presence of sulfuric acid; **3–6** in the presence of lithium perchlorate, and **5–7** in the presence of *p*-toluenesulfonic acid. Hydrolysis of the same substrate and its reaction with trichloroacetic acid characteristically give rise to analogous varieties of products having analogous structures. In the absence of acids, the reaction pattern is clearer and is determined by sterically more favorable rear attack by nucleophile at the less shielded carbon atom in the oxirane ring (Scheme 2).

Scheme 2.



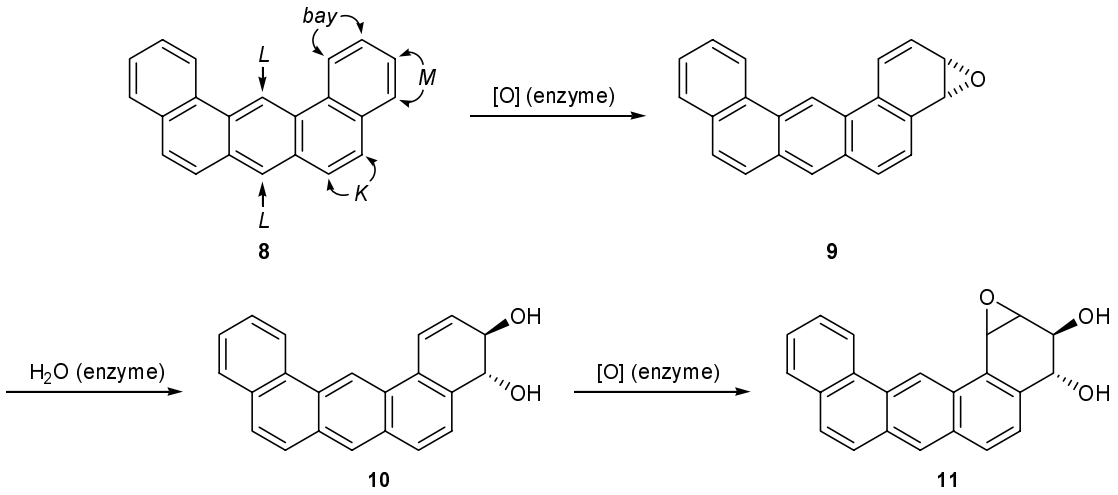
R = *t*-Bu (**a**), Ph (**b**), Bzl (**c**).

In the last decade, much attention was given to reactions involving chiral [9, 10] and naturally occurring epoxy compounds [11], desymmetrization of racemic epoxides, heterocyclization of products formed by reactions of epoxy derivatives with oxygen-containing nucleophiles, and development of synthetic approaches to biologically active compounds on the basis of hydrolysis products.

2. BIOLOGICAL ROLE OF EPOXY COMPOUNDS AND THEIR DERIVATIVES

Epoxy compounds play an important role in biology [12]; they are potential toxic intermediates in biotransformations of aromatic compounds and olefins.

Scheme 3.



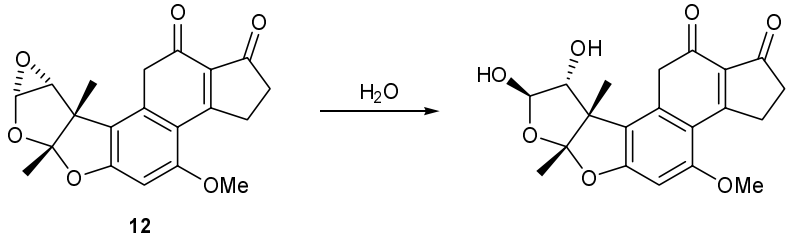
On the other hand, some 1,2-epoxy derivatives are effective mutagenesis and carcinogenesis inhibitors, as well as compounds possessing other kinds of biological activity [13]. Epoxy compounds are key intermediate products in the synthesis of many biologically important substances, and their further transformations often involve alcoholysis. Taking the above stated into account, epoxy derivatives and their reactions with alcohols, water, and acids have become subjects of strong and persistent interest of organic chemists.

Considerable attention is also given to the chemistry of epoxy diols derived from polycyclic aromatic hydrocarbons, which play an important role in mutagenesis and carcinogenesis. Structural fragments of these hydrocarbons are characterized by different abilities to undergo enzymatic oxidation. For example, dibenzoanthracene **8** is a weakly carcinogenic symmetric polycyclic hydrocarbon whose molecule includes the following regions: *bay*, *K*, *L*, and *M* [14].

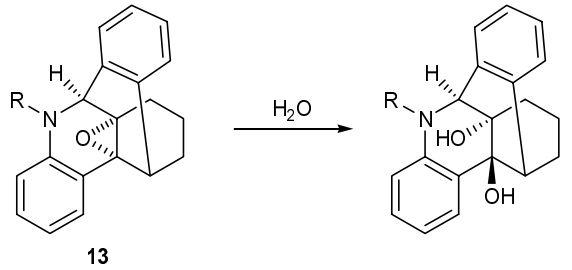
Enzyme-catalyzed oxidation of **8** primarily involves the *M* domain, the subsequent enzymatic hydrolysis of epoxy derivative **9** gives *trans*-diol **10**, and the latter is oxidized to epoxy diol **11** (Scheme 3). *Bay region* epoxy diols like **11** are capable of forming covalent adduct with DNA. The given scheme of metabolism is typical of a large number of aromatic hydrocarbons, benzo[*a*]pyrene [15], benzo[*c*]acridine [16], and quinoline and its analogs [17]. Though *bay region* tetrahydro epoxy compounds are not formed as intermediates in metabolic transformations of polycyclic aromatic hydrocarbons, they were synthesized and were shown to exhibit even stronger mutagenic activity than that intrinsic to related epoxy diols **11**. Both acid-catalyzed and spontaneous hydrolysis of both types of compounds is essentially facilitated due to carbocation stabilization by the neighboring aryl group. For example, acid hydrolysis of 9,10-epoxy *cis*-7,8-diol (benzo[*a*]pyrene metabolite) is faster by 4 orders of magnitude than analogous reaction with 1,2-epoxypropane. Similar relations are typical of spontaneous hydrolysis. Conjugation between the epoxy ring and aromatic system is important: the rate of acid hydrolysis of 1,2-epoxy-1,2,3,4-tetrahydronaphthalene is higher by a factor of 6×10^4 than the rate of analogous reaction of the corresponding nonconjugated epoxy compound.

Johnson *et al*. [18] studied the kinetics and mechanism of hydrolysis of Aflatoxin B_1 *exo*-8,9-epoxide (**12**) which is formed in living species by cytochrome P-450 and is very unstable in water ($\tau_{1/2} < 10$ s)

Scheme 4.



Scheme 5.



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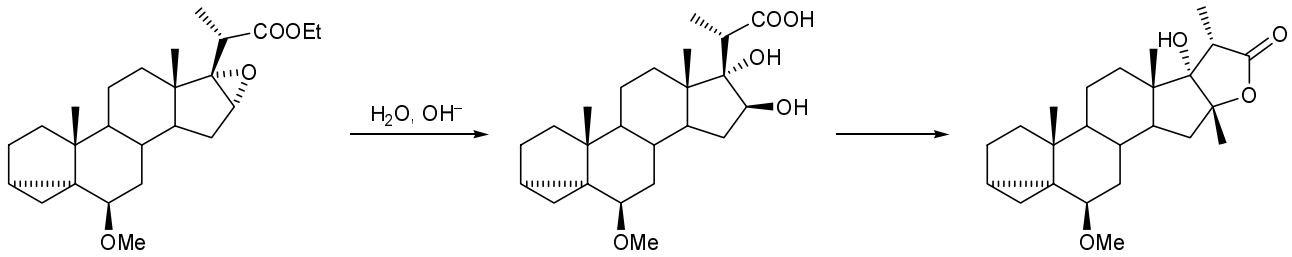
(Scheme 4). Aflatoxin B_1 is classed with difuranocoumarins and is thought to play a large role in human liver cancer. While developing synthetic approaches to the antitumor antibiotic Dynemicin A [19], acid-catalyzed hydrolysis [20] and isomerizations [21] of related epoxides were studied. The mechanism of action of Dynemicin A was simulated using various models [22–24], including epoxide **13** (Scheme 5); apart from water, methanol, phenol, and benzenethiol were used as nucleophilic agents [22]. Reactions of 16α,17α-oxidosteroids were examined with a view to search for new antitumor drugs [25] (Scheme 6).

Epoxycyclopentanes **15** and **16** were used as starting compounds to synthesize nucleotide analogs; here, the key stage was their hydrolysis [26, 27] (Scheme 7). Promising building blocks for the design of biologically active compounds were obtained on the basis of oxatricyclodecenones **17a**–**17c** [28] (Scheme 8).

Scheme 6.



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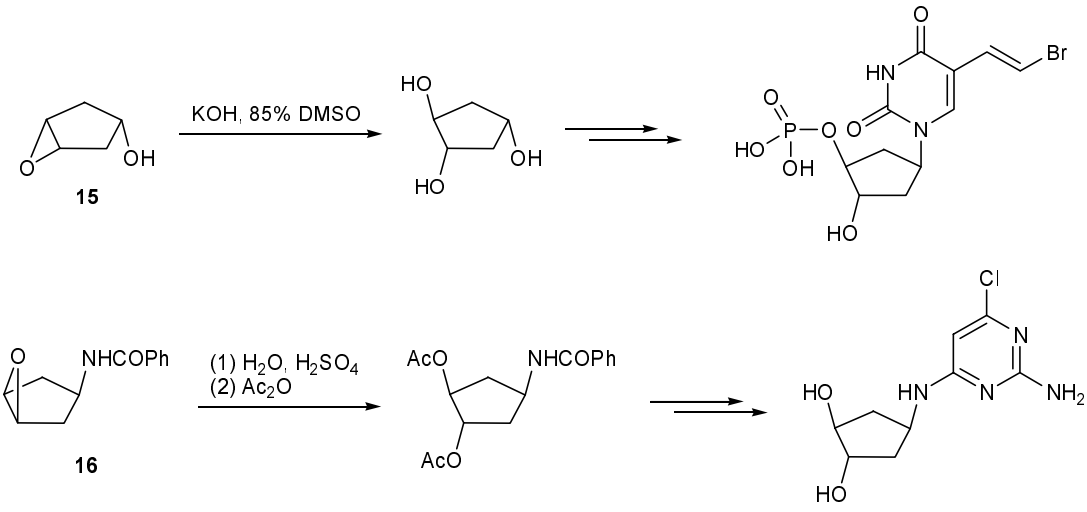
Scheme 7.



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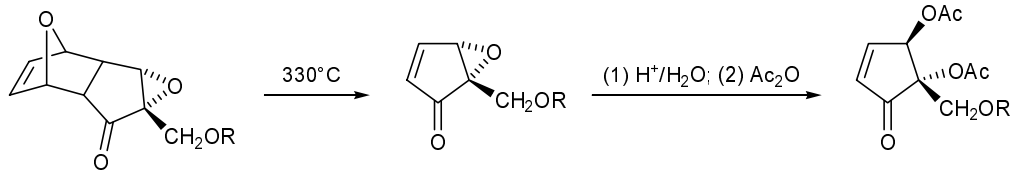
Scheme 8.

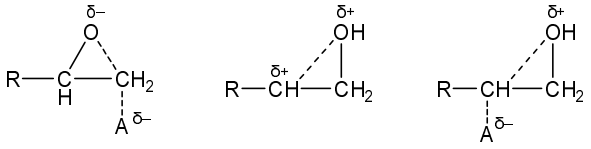


17a–17c

R = Me (**a**), Et (**b**), *i*-Pr (**c**).

3. MECHANISMS OF REACTIONS OF EPOXY COMPOUNDS WITH OXYGEN-CENTERED NUCLEOPHILES

There are numerous reports on the mechanisms of reactions of epoxy derivatives with water, acids, and alcohols in different media; possible transition states **18**–**20** were discussed in [29, 30].



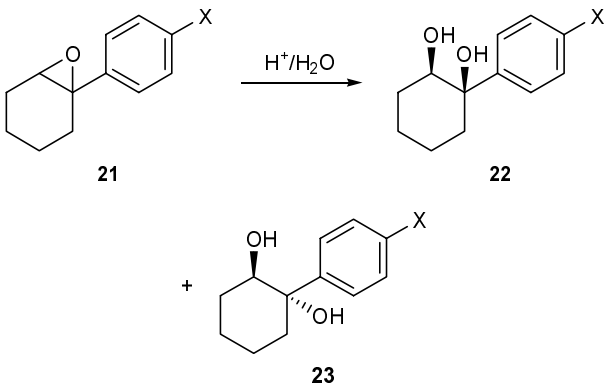
18 (S_N2) **19** (S_N1) **20** (S_N2')

The known general principles of epoxide ring opening in combination with available kinetic data imply that reactions involving transition state **18** follow the bimolecular nucleophilic substitution (S_N2) pattern typically accompanied by Walden inversion of the reaction center. Carbocationic mechanism (S_N1, transition state **19**) was previously presumed to be possible for acid-catalyzed reactions. It was confirmed primarily by violation of the Krasusky rule, i.e. by formation of a larger or smaller amount of the anomalous epoxide ring opening product.

The reaction mechanism proposed by Parker and Isaacs [29] turned out to be the most recognized by chemists. This model rationalized specific features of acid-catalyzed epoxide ring opening using a boundary S_N2 or S_N2' mechanism (transition state **20**).

Stereochemical specificity of the oxirane ring opening in epoxycycloalkanes is the formation of *trans*-coplanar transition state as a result of axial attack by nucleophile at one carbon atom of the oxirane ring, followed by inversion of configuration of that center (Fürst–Plattner rule) [31].

Scheme 9.

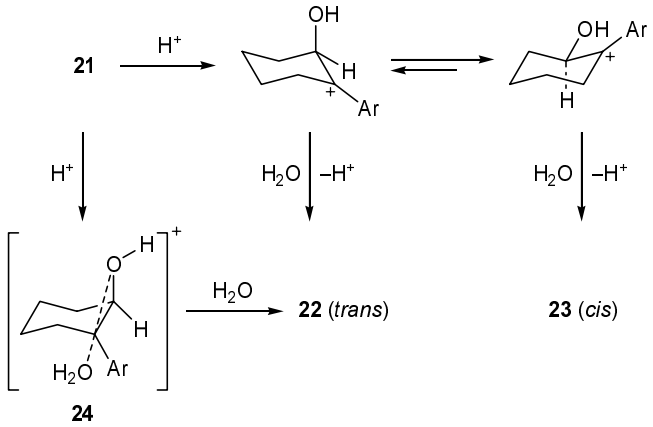


21 **22** **23**

X	MeO	Me	H	NO_2
22, %	95.5	83	63	7.5
23, %	4.5	17	37	92.5

Violation of *trans*-stereoselectivity toward *cis*-addition is frequently observed in the series of aryloxiranes [3]. Competition of *cis*- and *trans*-opening of epoxy ring was studied in detail for epoxy derivatives of arylcyclohexenes, and the results were shown to depend on numerous factors. Doan *et al*. [32] recently examined the effect of *para*-substituent in the benzene ring on the stereochemistry of hydrolysis of 1-aryl-1,2-epoxycyclohexanes **21** [32] (Scheme 9). The ratio of *cis*–*trans*-diols **22**:**23** rises as electron-donor power of the X substituent increases. The reaction mechanism includes formation of a carbocationic intermediate with subsequent attack by nucleophile (water) on both stereoisomeric carbocations. According to the authors, the ratio of alternative hydrolysis products is governed by their thermodynamic stabilities. The presence of a strong electron-acceptor group (such as nitro group) in the *para* position of the benzene ring destabilizes intermediate carbocation; in this case, *trans*-diol **23** is formed via concerted mechanism involving transition state **24** (Scheme 10).

Scheme 10.



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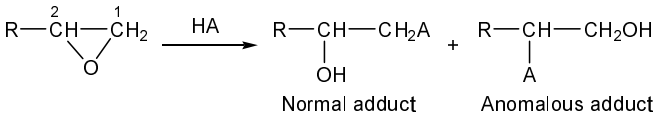
Another important characteristic of nucleophilic reactions of epoxy derivatives is their regioselectivity which conforms to the Krasusky rule discovered while studying aminolysis of alkyl-substituted oxiranes. This rule implies preferential formation of a more substituted alcohol among those possible [31]. The regioselectivity is controlled by steric factor: attack by nucleophile on the less substituted and more spatially accessible carbon atom (most frequently terminal carbon atom) of the epoxide ring (C^1) is preferred

[29, 33]. Reactions occurring in acid medium are characterized by a considerable probability for nucleophilic attack to be directed at C^2, leading to formation of "anomalous" products (Scheme 11).

Scheme 11.

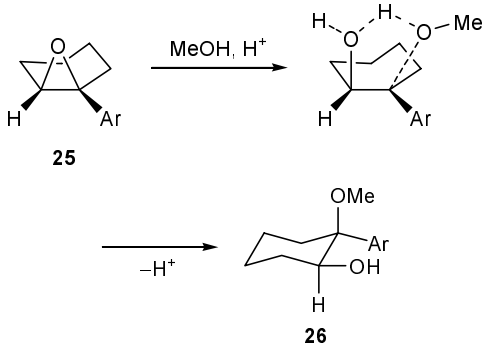


Later on, Crotti *et al*. studied for many years reactions of epoxycyclohexanes with various nucleophiles in alkaline and acid media and proposed a more perfect transition state for methanolysis (hydrolysis); the authors convincingly showed that *cis*-opening of the epoxide ring follows an ion–dipole mechanism [34]. On the basis of vast experimental data, the same authors performed a series of fundamental studies [8, 35–38] on the effect of various factors on the stereo- and regioselectivity of oxirane ring opening in the series of conformationally labile 1-aryl-, 1-benzyl-, 1-alkyl-, 1-ethynyl-, and 1-trimethylsilyl-1,2-epoxycyclohexanes with alcohols, acids, and water. Opening of the epoxide ring is preceded by protonation of the oxirane oxygen atom, followed by partial or complete cleavage of the carbon–oxygen bond. Different carbocationic intermediates thus formed give rise to either 1,2-adducts as a result of attack by nucleophile or elimination and rearrangement products, their ratio depending on the epoxide structure and reaction conditions. If an aryl group, double bond, or another unsaturated system is directly attached to the oxirane ring, the reaction in acid medium may follow different paths characterized by a stereoselectivity from complete *anti* to almost complete *syn*. Although predominant *anti*-attack is typical of cycloaliphatic oxiranes, a small amount of the corresponding *syn* adduct is formed even from 1-methyl-1,2-epoxycyclohexane. This result indicates that methyl group is capable of stabilizing a tertiary carbocationic center according to the inductive or hyperconjugation mechanism.

However, aryl substituents change the stereochemical outcome of epoxide ring opening most strongly. For example, acid-catalyzed methanolysis of 1-aryl-1,2-epoxycyclohexanes **25** leads to formation of a considerable amount of *syn*-adduct **26** whose yield may attain even 90% [35] (Scheme 12).

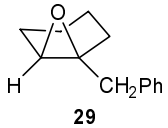
The stereochemistry of epoxide ring opening in conformationally labile epoxy derivative **25** and its behavior in methanolysis was compared with those

Scheme 12.



observed for more rigid stereoisomeric *cis*- and *trans*-analogs **27** and **28** having a *tert*-butyl group in position *4* of the cyclohexane ring. Taking into account similar behaviors of compounds **28** and **25**, it was presumed that the former reacts in a *half-chair* conformation (which is analogous to the conformation of **25**) and that "axial" opening of the epoxide ring leads to a structure with an axial hydroxy group. These findings were used in the discussion on the known Fürst–Plattner rule [31].

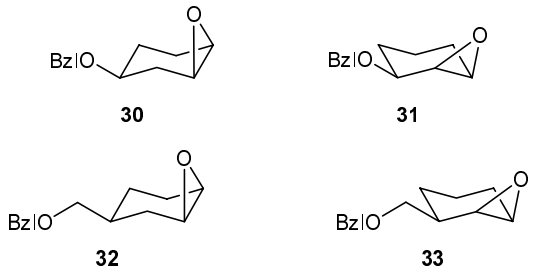
Methanolysis of 1-benzyl-1,2-epoxycyclohexane (**29**) also afforded the corresponding *syn*-adduct whose fraction was even greater than in the reaction with the 1-methyl-substituted analog. Therefore, the authors [36] convincingly postulated participation of the aryl fragment in the benzyl substituent and proposed a mechanism involving intermediate formation of phenonium ion.



Undoubtedly, it was interesting to compare the results of acid-catalyzed solvolytic and gas-phase methanolysis of 1,2-epoxy-1-phenylcyclohexane [39, 40]. The corresponding oxonium ion was obtained by the action of gaseous acids, such as D_3^+ and $C_nH_5^+$ (n = 1, 2), which were generated by γ-radiolysis of neutral precursors (D_2, CH_4).

The regioselectivity of gas-phase methanolysis of epoxycyclohexanes, in which substituents are remote

from the oxirane ring, was studied in [41]. *cis* Isomers **30–33** of these compounds are shown below.

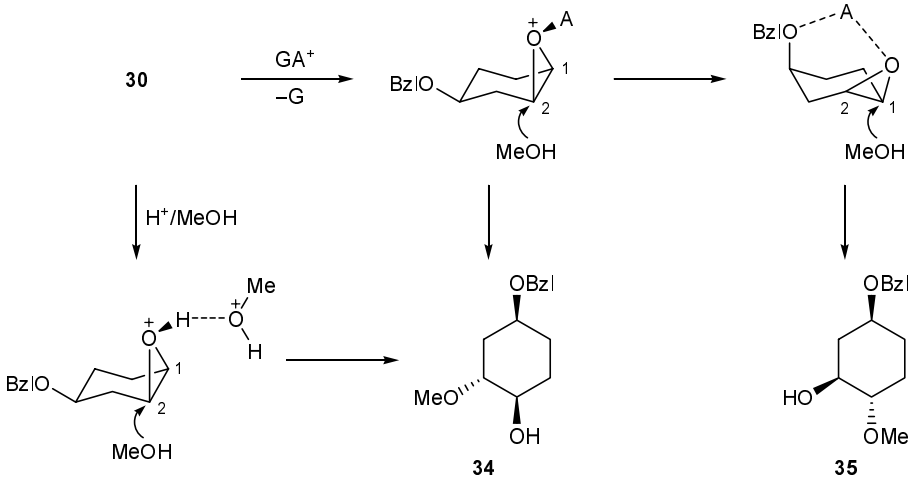


The results showed that their gas-phase reactions involved bidentate chelating species which were not formed when the methanolysis was performed in the liquid phase. Scheme 13 illustrates different regioselectivities of methanolysis of 4-benzyloxy-1,2-epoxycyclohexane (**30**) in the liquid and gaseous phases; here, **34** is the normal product, and **35** is that formed as a result of gas-phase chelation. Unusual methanolysis products were also formed from *cis*-epoxides **30–33** in the liquid phase in the presence of lithium perchlorate as chelating species. Presumably, proton acquires chelating ability in gaseous phase, while it lacks such ability in solution [41].

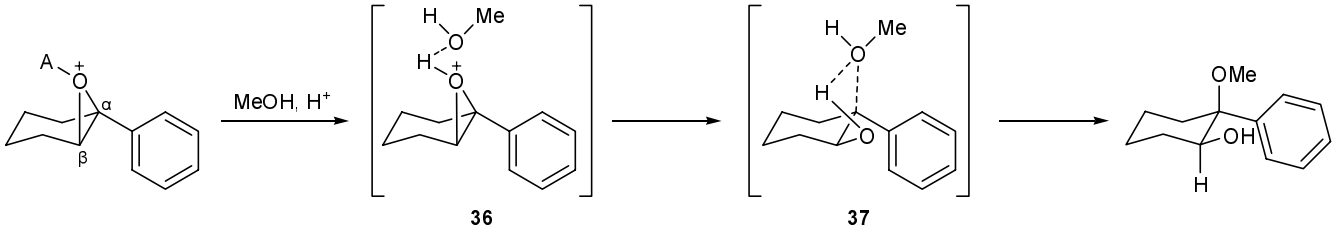
Usually, *syn*-addition of a nucleophile was rationalized in terms of stabilization of partial positive charge on the C^{α} atom in the transition state due to electron-donor effect of the phenyl group. The results of gas-phase methanolysis of epoxy compounds in which substituents in the benzene rings are capable of affecting charge delocalization (*m*-Cl, *p*-NO_2) may be regarded as experimental support of the above hypothesis. In fact, as the electron-acceptor power of the substituent rises, the stereoselectivity of nucleophilic attack by methanol sharply changes from frontal *syn* (91–100%) to 70–87% rear for *m*-chlorophenyl derivative and completely rear (100%) for *p*-nitrophenyl analog [40]. The regioselectivity also changes: in the reactions with the two former epoxy derivatives (H, *m*-Cl), nucleophilic attack is directed at the C^{α} atom, while *p*-nitrophenyl-substituted compound undergoes attack by methanol on C^{β} as well (20–32%). According to [40], a possible factor favoring the *syn*-attack is facile isomerization of adduct **36** into entropy-preferred structure **37** which then decomposes with formation of the *syn*-adduct (Scheme 14).

In 1990, Iranpoor and Baltork [42] proposed an ion–radical mechanism for a reaction catalyzed by cerium(IV) ammonium nitrate (Scheme 15); the reaction of epoxy derivatives with primary, secondary, and tertiary alcohols occurs under mild conditions through intermediate **38**. Mixed cerium and ammonium salts

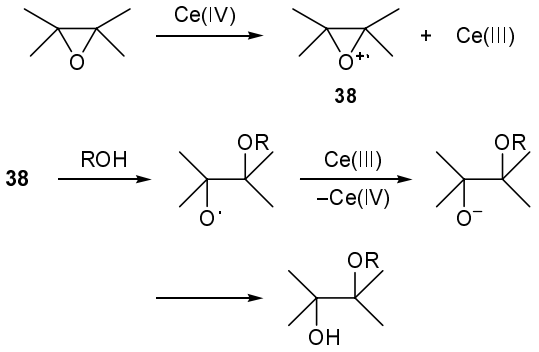
Scheme 13.

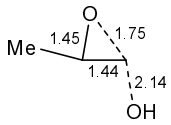


Scheme 14.



Scheme 15.





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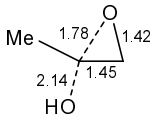

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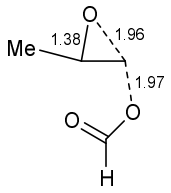

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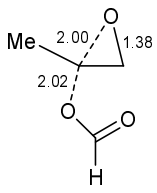


42

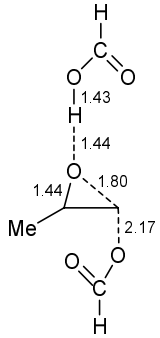
were later replaced by silver trifluoromethanesulfonate which ensured 80–95% yields in reactions of epoxycyclohexanes, epoxycyclopentanes, and epoxycyclooctanes with methanol, ethanol, and 2-propanol [43].

Mechanisms of epoxide ring opening with oxygen-centered nucleophiles were also studied by quantum-chemical methods [44–48]. The reactions of methyloxirane with hydroxide and formate ions were examined *ab initio* [MP4(SDQ)/6-31+G**//MP2/6-31+G**] and in terms of the density functional theory (DFT) [48]. This system was used to simulate covalent binding of an epoxide inhibitor to glycosidase active centers, and the results turned out to be helpful in the development of the theory of enzyme-catalyzed opening of oxirane ring.

The reactions of methyloxirane with hydroxide [45] and formate ions [46] and of *trans*-1-methyl-2-phenyloxirane with acetate ion [47] were studied on the nonempirical Hartree–Fock (HF), MP2, and DFT (B3LYP) levels. The HF calculations gave considerably overestimated (by almost 50%) E_a values, as compared to the B3LYP and MP2 procedures which take into account electronic correlation. More precise consideration of electronic correlation in terms of the fourth-order Moeller–Plesset theory [MP4(SDQ) approximation] gives energies of activation almost identical to those obtained by the MP2 calculations. The reaction of methyloxirane with OH^- ion (which is a stronger nucleophile than formate ion) is characterized by a lower activation barrier; the transition state in the reaction with formate ion may be regarded as later. In both cases, transition states **39** and **40** corresponding to nucleophilic attack on the primary carbon atom are more compressed.

A strong interest is attracted by a series of recent nonempirical quantum-chemical studies on the mechanisms of epoxide reactions catalyzed by formic acid [46] and one- [47, 49] and twohydric alcohols and phenols [49]. Gas-phase reactions of formate ion with the complex methyloxirane–formic acid, involving attack by the nucleophile on the primary (structure **43**) and secondary (**44**) carbon atoms of the oxirane ring, are characterized by activation energies E_a of 28.0 and 36.0 kJ/mol, respectively [B3LYP/6-31+G(*d*,*p*) calculations] [46]. If solvent effect is taken into account [B3LYP/6-31+G(*d*,*p*)/IPCM-HF/6-31+G(*d*,*p*)], the E_a values are 40.5 and 56.3 kJ/mol, respectively. Thus opening of the three-membered ring in methyloxirane molecule in the presence of formic acid follows the Krasusky rule, as in the absence of acid activation. The presence of acid catalyst reduces the activation barriers to alternative reaction paths by 37.0 and 40.0 kJ/mol in the gas phase and by 28.0 and 23.0 kJ/mol if solvent effect is taken into account. The energy of activation of the phenol-catalyzed reaction of *trans*-1-methyl-2-phenyloxirane with acetic acid also decreases on the average by 40.0 kJ/mol, as compared to the noncatalyzed reaction [47]. The energies of activation calculated on the MP2/6-31+G(*d*,*p*)//HF/6-31+G(*d*,*p*) and B3LYP/6-31+G(*d*,*p*)//HF/6-31+G(*d*,*p*) levels are, respectively, 43.5 and 38.5 kJ/mol for attack on the benzylic carbon atom and 47.3 and 45.2 kJ/mol for attack on the secondary carbon atom.

The crucial role of solvent effect was noted while studying the reactivity of stereoisomeric *exo*- and



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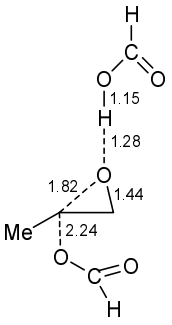
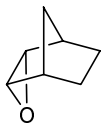


44

Calculated geometric parameters (interatomic distances and bond and torsion angles) of transition states for epoxide ring opening in epoxynorbornanes **45** and **46** and the corresponding activation barriers

Epoxide no.	$d(C–O^1)$, Å	$d(C–O^2)$, Å	$\angle CCO^1$, deg	$\angle O^1CO^2$, deg	$\varphi(O^1CCO^2)$, deg	$\Delta H^{\neq}$, kJ/mol
Gas phase						
45	1.854	2.058	80.3	144.0	–142.7	141.2
46	1.876	2.064	81.5	144.4	–144.9	135.6
Macroscopic approximation						
45	1.893	2.155	82.2	139.3	–137.2	169.7
46	1.981	2.292	87.0	137.0	–136.8	172.1
Supermolecular approximation						
45	2.046	2.298	91.1	143.7	138.8	205.2
46	2.078	2.205	92.8	134.5	124.3	214.9

endo-epoxynorbornanes **45** and **46** [50]. Although the kinetic parameters of alkaline methanolysis of these compounds indicated higher reactivity of *endo* isomer **45** [51], calculations performed for the gas phase erroneously predicted higher reactivity of *exo* isomer **46** [50]. Presumably, this is the result of underestimation of steric factor which becomes considerably more important for reactions of epoxides with solvated methoxide ion. Insofar as experimental study of base-catalyzed methanolysis was performed in methanol which is a fairly polar solvent capable of forming hydrogen bonds, the effect of the solvent was analyzed in two ways: with account taken of nonspecific solvation in macroscopic approximation (COSMO approach) [52] and using a supermolecule model which was developed for the first time while studying alkaline methanolysis of epoxyethane [53]. The first approach led to transition states characterized by a lesser degree of O^2–C bonding and greater degree of $C–O^1$ bond breaking, as compared to the corresponding data obtained for the gas phase; i.e., the transition states are looser. Both reactions are characterized by increased E_a values due to lower stabilization of the transition state (electron density delocalization in the transition state is stronger than in the encounter complex). Analogous trends were revealed previously by nonempirical calculations of the reactions of methyloxirane with formate ion and of *trans*-1,2-epoxy-1-phenylpropane with acetate ion [45–47]. When only nonspecific solvation was taken into account, no appreciable improvement of the agreement between the calculated E_a values and kinetic parameters was achieved. Although the *endo* isomer is more reactive among the two stereoisomeric epoxynorbornanes, the difference between the calculated activation barriers is as small as 2.4 kJ/mol (see table), which is not fully consistent with the experimental data [51].



45

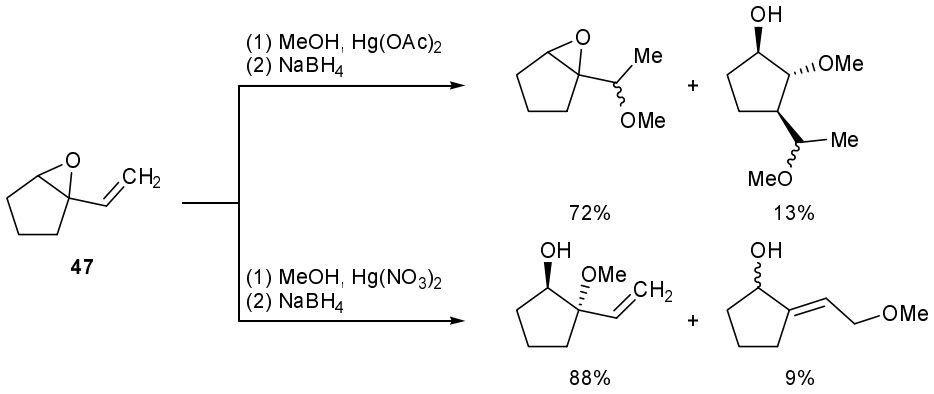
46

In terms of the supermolecule model, the first solvate shell includes eight methanol molecules: four molecules for methoxide ion and the same for oxirane. Further increase in the number of solvent molecules does not lead to an appreciable variation of the activation barrier. Localized transition states are looser than those calculated for the gas phase and for solution in the macroscopic approximation (see table). According to the supermolecule approximation, the barrier to activation in the reaction of *endo* isomer **45** is considerably lower (by 9.6 kJ/mol) than that found for *exo* isomer **46**. Comparison of these data with the results obtained for the gas phase indicates that steric factor is crucial in the estimation of the reactivity of strained epoxynorbornanes **45** and **46**. Just that factor was additionally taken into account while using the supermolecule model which involves solvent molecules in the explicit form; therefore, the size of the attacking species considerably increases [50].

4. CATALYSTS IN REACTIONS OF EPOXY COMPOUNDS WITH WATER AND ALCOHOLS

Catalyst nature is important in reactions of epoxides with alcohols. Chemoselective transformation of either double bond or epoxy fragment was observed [54] in

Scheme 16.



the reaction of 1,2-epoxy-1-vinylcyclopentane (**47**) with methanol in the presence of mercury acetate and mercury nitrate, respectively (Scheme 16). The authors believe that ionic nature of mercury nitrate favors activation of nucleophilic center in the epoxide and that mercury acetate acts as a conventional oxymercurating agent.

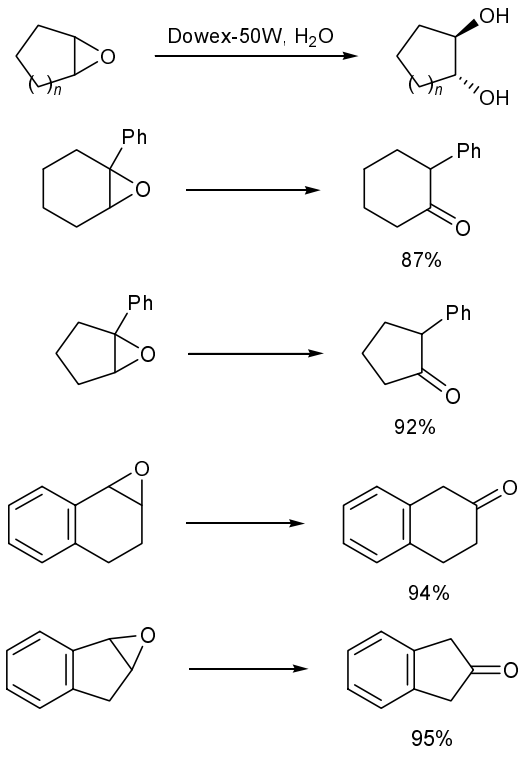
Alcoholysis of epoxides was performed using various acids [55], including those generated electrochemically [56], iodine compounds, e.g., iodine-containing poly(vinylpyrrolidinones) [57], iron trifluoroacetate [58], fluorine-containing titanium compounds [59], copper tetrafluoroborate [60], lithium perchlorate [61], and molybdenum and tungsten heteropolyacids [62]. The latter turned out to be more active than sulfuric and perchloric acids. Among the examined molybdenum and tungsten catalysts, namely $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, and $H_4SiW_{12}O_{40}$, the former was the most active, and the catalytic activity of these compounds did not change during the process.

Iron(III) chloride seems to be quite promising and important; it promotes stereoselective *trans*-opening of epoxycyclohexane, epoxycyclopentane, and epoxyindan derivatives. The reaction mechanism was not studied; nevertheless, Iranpoor and Salehi [63] presumed formation of a radical cation in the first step. Silica-supported iron(III) chloride hexahydrate was shown [64] to catalyze alcoholysis, hydrolysis, and acetolysis with high stereo- and regioselectivity and high yield.

Fused organotin phosphates were also tested as catalysts for alcoholysis of epoxy compounds; they were used to activate reactions of both epoxycycloalkanes and epoxy derivatives of acyclic alkenes, including functionally substituted compounds [65]. Tin–cobalt compounds made it possible to perform reactions with secondary and tertiary alcohols with high selectivity [66]. In 2001, Salomon [67] described a new tin-containing catalyst, bis-chlorodibutyltin oxide, which promoted anti-Krasusky addition of alcohols to epoxides; alternative regioselectivity was observed in the reaction with 1,2-epoxy-3-phenoxypropane.

Another group of catalysts for alcoholysis of epoxides includes aluminosilicates [68]; a mixture of Al_2O_3 with $AlPO_4$ catalyzed not only alcoholysis but also reactions with water, thiols, and benzoic acid [69]. Aluminum oxide is known to catalyze reactions of epoxy compounds with hydroperoxides [70] and carboxylic acids [71]. For example, aluminum oxide ensures stereospecific transformation of epoxycyclo-

Scheme 17.



octane into *trans*-2-acetoxycyclooctanol, whereas only 22% of the target product was isolated from the mixture of products obtained by homogeneous solvolysis.

Cation exchangers like Dowex-50W [72] were successfully used as catalysts; C_5–C_7 epoxycycloalkanes were thus converted almost quantitatively into the corresponding *trans*-diols, and 1-aryl-1,2-epoxy compounds were converted into aryl ketones in high yield (Scheme 17).

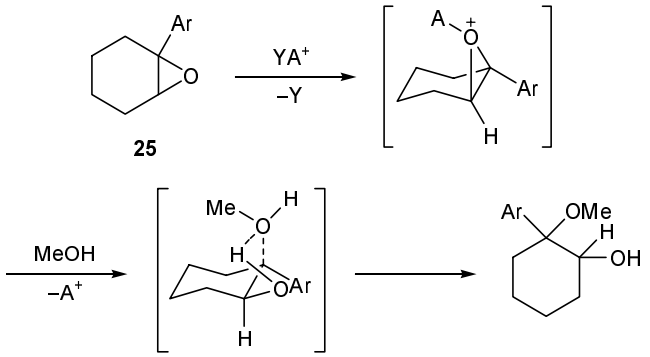
Hydrolytic cleavage of epoxides was performed using bentonite [73]. Epoxy derivatives of steroids were converted into the corresponding vicinal diols in anhydrous benzene at 50°C, and the catalyst turned out to be more efficient than many others, such as aluminum oxide, silicon oxide, etc. The reactions of epoxycyclohexane with methanol and benzyl alcohol and of epoxycyclopentane with methanol, as well as hydrolysis of both epoxides, were studied in the presence of Nafion-H (a polymeric perfluorinated sulfonic acid). In all cases, the products had *trans* configuration. Hydrolysis of epoxyindan was characterized by a high yield. 1-Phenyloxirane reacted with methanol contrary to the Krasusky rule, while the reaction with 1-methyloxirane mainly followed that rule (by 88%). However, the application of this efficient catalyst is limited due to its acidic nature which is often incompatible with high sensitivity of oxiranes [74].

Tetracyanoethylene occupies a specific place among compounds catalyzing alcoholysis of epoxides. Its π-acceptor character favors reactions of epoxy compounds with methanol, 2-propen-1-ol, phenylmethanol, and 2-propanol to occur under mild conditions with a yield of 70–97% [75, 76].

One of the known methods for activation of epoxide ring is related to gas-phase reactions of oxiranes, which were studied since 1980s [77]. Various gaseous products (D_3^+, CH_5^+, $C_2H_5^+$, etc.) resulting from γ-radiolysis of neutral compounds were used as catalysts. Crotti *et al*. [78] studied in parallel liquid-phase and gas-phase methanolysis of 1-aryl-1,2-epoxycyclohexanes **25** in acid medium and found that both reactions follow a common ion–dipole mechanism [79] (Scheme 18). The formation of ion–dipole complexes in gas-phase reactions was confirmed by quantum-chemical studies; also, increased probability for elimination in the gas phase as compared to liquid phase was shown [45].

In 1990s, cerium-based catalysts were proposed for reactions of epoxides with water and acetic acid under mild conditions. Initially, mixed cerium and ammo-

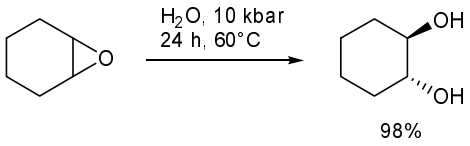
Scheme 18.



nium nitrate was used [80]. Tris[trinitrato-Ce(IV)-paraperiodate] [81] showed excellent results in the hydrolysis and acetolysis in acetonitrile solution, and cerium trifluoromethanesulfonate effectively catalyzed reactions of thiiranes as well [43]. A radical ion mechanism was proposed for the transformations of epoxy compounds and thiiranes [43, 81].

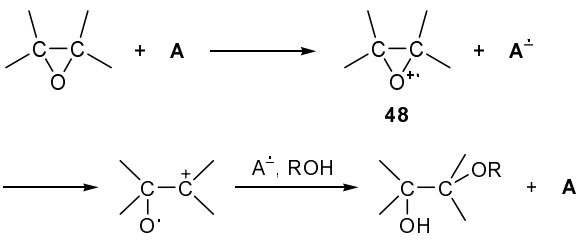
Some unusual hydrolysis procedures must be noted, primarily stereoselective high-pressure hydrolysis with no catalyst [82] (Scheme 19). Shevchenko *et al*. [83] reported on photoinitiated reaction of oxiranes with carboxylic acids in the presence of triphenylsulfonium hexafluorophosphate(V).

Scheme 19.

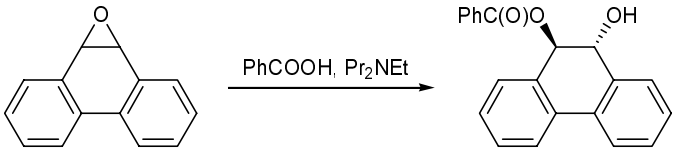


Most of the above described procedures are applicable only to primary alcohols. A general method ensuring cleavage of epoxide ring by the action of primary, secondary, and tertiary alcohols in neutral medium was proposed in 1990 by Iranpoor and Baltork [84]; the authors utilized 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (**A**) as catalyst (Scheme 20). Under these conditions, epoxycyclohexane reacted with alcohols (from methanol to *tert*-butyl alcohol) in 0.5–4 h

Scheme 20.



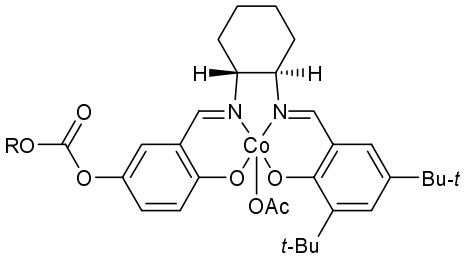
Scheme 21.



49 *ee* 93%

to afford 85–95% of the corresponding alcoholysis product. According to the authors, the reaction with unsymmetrically substituted oxiranes was strictly regioselective (1-chloro-2,3-epoxypropane and 1-allyloxy-2,3-epoxypropane reacted according to the Krasusky rule, and 1-phenyloxirane, contrary to it), but no proofs for perfect regioselectivity were given. The reaction was presumed to follow single-electron transfer pattern with intermediate formation of epoxonium radical cation **48**.

Participation of nitrogen-containing ligands in homogeneous and heterogeneous catalysis of various reactions, including reactions of epoxy compounds, was reviewed in [85]. For example, cobalt(II) complexes were successfully used to catalyze the reaction of epoxydihydrophenanthrene (**49**) with benzoic acid (Scheme 21). Cobalt-containing chiral compounds **50** [85], **51** [86, 87], and **52** (X = *p*-$CF_3C_6H_4COO$, PF_6, BF_4, CF_3SO_3, *p*-$CH_3C_6H_4SO_3$, SbF_6, Br, I) [88] are known as catalysts of hydrolysis of epoxy derivatives. These catalysts made it possible to effect kinetically controlled resolution of racemic oxiranes (Scheme 22; R = Et, Bu, *i*-Pr, Ph, CH_2Cl). Desymmetrization of centrosymmetric diepoxide **54** was performed in the presence of catalyst **51** [86] (Scheme 23). Manganese-containing compounds catalyzed hydrolysis of epoxides [85], and reactions of epoxy compounds with phenols were performed in the presence of gallium catalysts [89].



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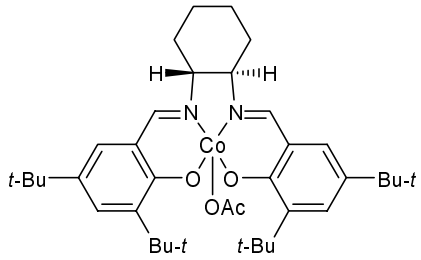

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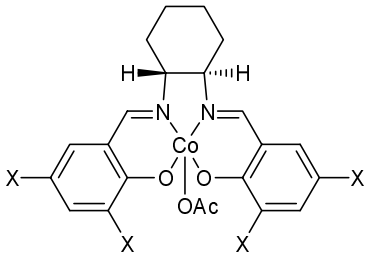
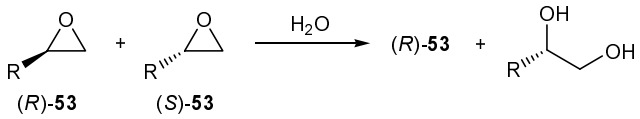
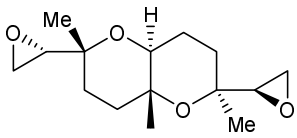


52

Scheme 22.



Scheme 23.



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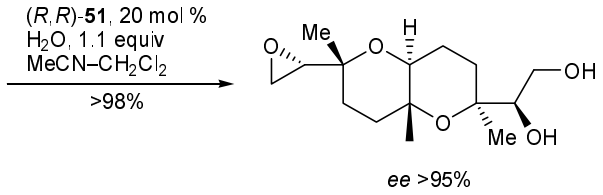


ee >95%

In 1990s, Chen *et al*. [90] described first examples of enantioselective or diastereoselective hydrolysis of epoxy compounds on a multigram scale in the presence of *Aspergillus niger* containing intracellular epoxide hydrolase (EH). The results were improved by carrying out the process under anaerobic conditions; procedures for the preparations of all four bisabolol stereoisomers were given.

A series of important and interesting studies on enzymatic catalysis of hydrolysis of alicyclic epoxides

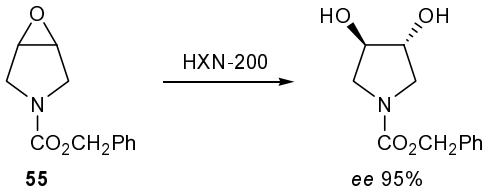
was performed [91, 92]. Hydrolysis of alicyclic epoxy compounds was catalyzed by epoxide hydrolase (EH) which is an important enzyme involved in metabolism of mutagenic and carcinogenic epoxides, including those formed by oxidation of alkenes and aromatic xenobiotics with cytochrome P-450 monooxygenase. Chemoenzymatic procedures for the synthesis of optically active substances from racemic and optically pure alicyclic epoxy compounds were developed [93].

In 1997, Archer reviewed the data on various epoxide hydrolases and mechanisms of their action as asymmetric catalysts [94]. The structure of epoxide hydrolases was described in [95].

Microsomal and cytosol forms of epoxide hydrolase from rabbit liver were successfully differentiated. The first of these is widely used for enantioselective transformations of various substrates. In particular, catalytic opening of oxirane ring occurs predominantly (with only a few exceptions) at a carbon atom having *S* configuration. Both enzyme forms were used to catalyze hydrolysis of epoxycycloalkanes derived from cyclopentene, cyclohexene, cycloheptene, and cyclooctene; enantioselective cleavage of the carbon–oxygen bond in alicyclic *meso*-epoxides gave levorotatory glycols with a high enantiomeric excess.

Enantioselective hydrolysis of *N*-phenoxy- and *N*-benzyloxycarbonyl-3,4-epoxypyrrolidines **55** and *N*-substituted 1,2,5,6-tetrahydropyridines was performed with the aid of bacterial epoxide hydrolase [96, 97] (Scheme 24).

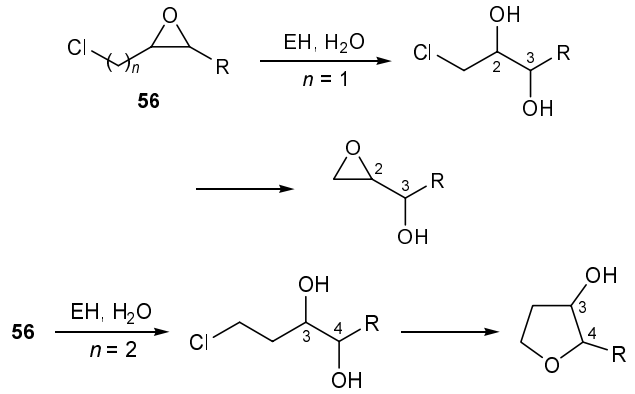
Scheme 24.



Analogous experiments were successful with alkenyl- [98] and haloalkyloxiranes **56** [99]; in the latter case, cyclic systems were obtained as a result of spontaneous elimination (Scheme 25).

Reetz *et al*. [100] described the hydrolysis of 1,2-epoxy-3-phenoxypropane in the presence of epoxide hydrolase isolated from *Aspergillus niger*; the same enzyme was used for hydrolytic kinetic resolution of epoxides [101]. Berili *et al*. studied [102] enzymatic hydrolysis of (±)-3,4-epoxytetrahydropyran, a series of stereoisomeric analogs of epoxy sugars, and other

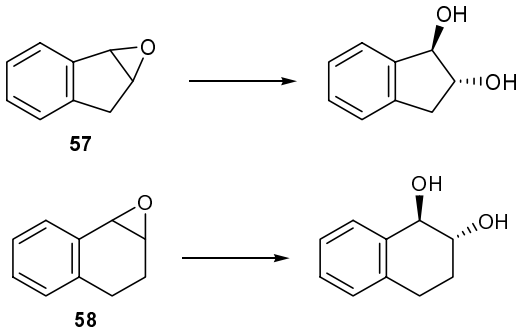
Scheme 25.



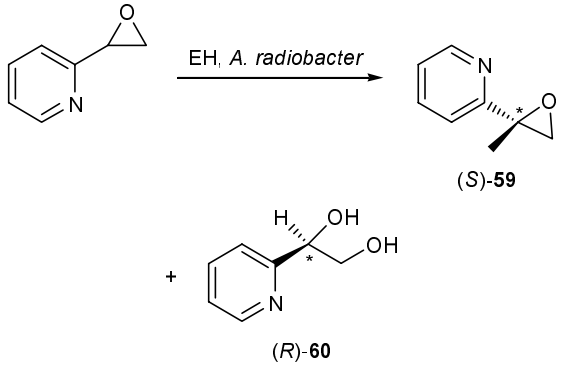
compounds. The stereochemical data thus obtained provided a supplement to previous proofs for general base catalysis in enzymatic reactions. Enzymatic processes constituted particular stages in asymmetric syntheses of natural compounds [103].

Microbiological transformations of epoxides were effected with the aid of fungal epoxide hydrolase. Hydrolytic kinetic resolution of racemic epoxyindan **57** and epoxytetrahydronaphthalene **58** gave both optically pure epoxides (*ee* 98%) and the corresponding diols (*ee* 69 and 77%, respectively) [104] (Scheme 26). Enantioselective biohydrolysis of 2-, 3-, and 4-pyridyloxiranes was reported in [105, 106]. As in the above

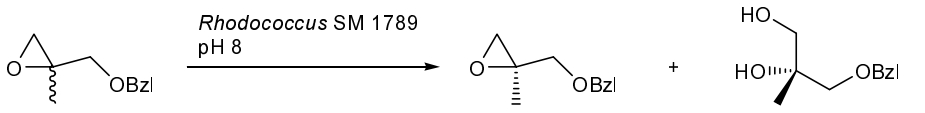
Scheme 26.



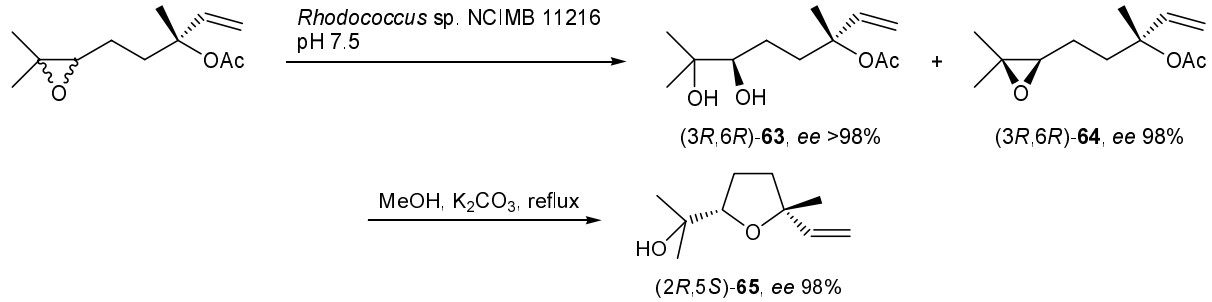
Scheme 27.



Scheme 28.



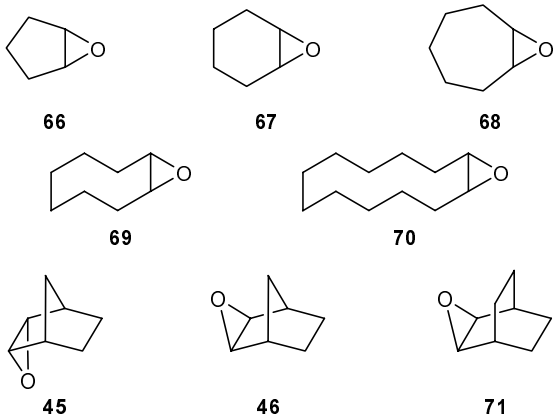
Scheme 29.



examples, kinetic resolution of these epoxy compounds was achieved via stereoselective epoxide ring opening. As a result, one epoxide enantiomer **59** which is inert toward natural enzyme and hydrolysis product **60** of the second (active) enantiomer were isolated (Scheme 27). Bacterial epoxide hydrolases were successfully used in a number of reactions [92, 107], e.g., as shown in Schemes 28 and 29.

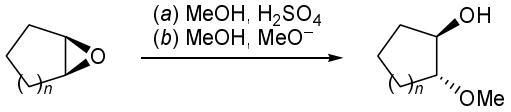
5. TRANSFORMATIONS OF EPOXY COMPOUNDS BY THE ACTION OF ALCOHOLS

Methanolysis of alicyclic epoxy compounds was described in [108] where the effect of strain in the alicyclic fragment on the reactivity of epoxides was studied. The kinetic parameters of methanolysis were given. Sharp difference in the reaction rates was observed for methanolysis in acid (dilute sulfuric acid) and alkaline media (sodium methoxide in methanol). In acid medium, all the examined epoxy compounds underwent methanolysis, though some derivatives



(epoxycyclooctane **69** and epoxycyclododecane **70**) reacted quite slowly; in basic medium, compounds **69** and **70**, as well as *exo*-epoxynorbornane **46**, failed to react [108]. The molar ratio epoxide–methanol–catalyst (concentrated sulfuric acid or sodium methoxide) was 1:250:0.0017 and 1:250:10, respectively. The use of a relatively large amount of sodium methoxide suggests an important role of effective electrophilic assistance in epoxide ring opening. The products obtained in different media were identical; all these were formed via *trans*-opening of the oxirane ring (Scheme 30).

Scheme 30.

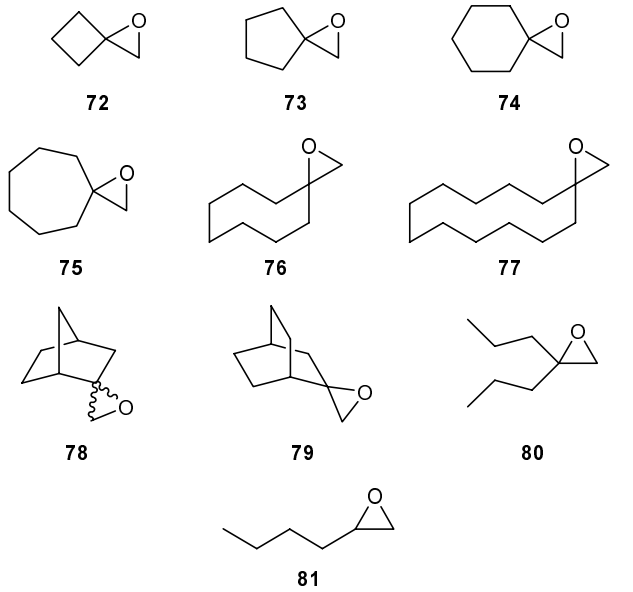


n = 1–4, 8.

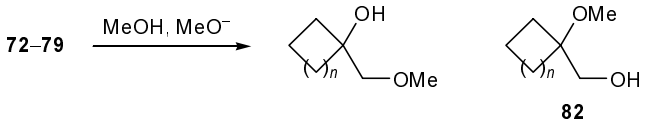
Acid-catalyzed methanolysis of epoxynorbornane **46** involves Wagner–Meerwein rearrangement which is accompanied by 2,6-hydride shift [109]. The major product of acid methanolysis of its stereoisomer **45** was isolated as the only one when the reaction was carried out under basic conditions; it resulted from *trans*-opening of the oxirane ring.

Methanolysis of 1-oxaspiro[2.*n*]alkanes **72–79** and epoxy compounds **80** and **81** with methoxide ion was regioselective (in keeping with the Krasusky rule) [110, 111]. Protonated complex formed in acid medium allows nucleophilic attack to be directed at the more sterically shielded oxirane carbon atom; therefore, methanolysis of epoxides **74** and **77** occurs predom-

inantly (by 60–70%) contrary to the Krasusky rule, yielding compound **82**, and is accompanied by formation of allyl alcohols [112] (Scheme 31).



Scheme 31.

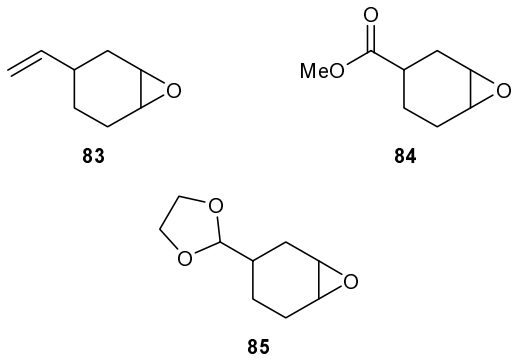


The effect of steric strain on the rate of methanolysis of cycloalkanes was studied by calorimetry [113] and molecular mechanics (MM2) [114], and the results were confirmed by comparison with the corresponding kinetic parameters [51, 115] in alkaline and acid media. Variation of the acidity did not change the reactivity series of epoxy compounds, while the reaction rate considerably increased as the acidity rose. The most reactive was epoxycyclohexane; the same pattern is typical of epoxide reduction with lithium tetrahydridoaluminate [116] and other reactions involving activation of the oxirane oxygen atom. Presumably, similar concerted methanolysis mechanisms are operative in both reaction media, but protonation activates the oxygen atom much more efficiently than does formation of hydrogen bond with methanol.

A narrower range of variation of the rate of methanolysis in the series of spiro epoxy compounds **72–79** was rationalized in terms of a weaker effect of the alicyclic fragment through only one common carbon atom of the spiro system [110, 112].

Quantum-chemical studies on the mechanism of alkaline methanolysis of epoxycycloalkanes [50] and epoxy derivatives of methylidenecycloalkanes [117] localized the transition states and encounter complexes. Enhanced reactivity of conformers with pseudoequatorial orientation of the methylene group was revealed in the series of conformationally labile spiro oxiranes [117]. Methanolysis of epoxides was simulated both in the gas phase and with account taken of solvent effect in macroscopic and supermolecular approximations [53]. A supermolecular model was developed, which properly allowed for contributions of electronic and steric factors. The calculated values of $\Delta H^{\neq}$ were consistent with the logarithms of the experimental rate constants of the corresponding reactions [50, 117].

Methanolysis of 4-substituted 1,2-epoxycyclohexanes **83–85** in acid and alkaline media was studied in [118]. The product composition was determined by gas–liquid chromatography, and electron density distribution in the substrate molecules and regioselectivity of the process were analyzed by PM3 quantum-chemical calculations [118].

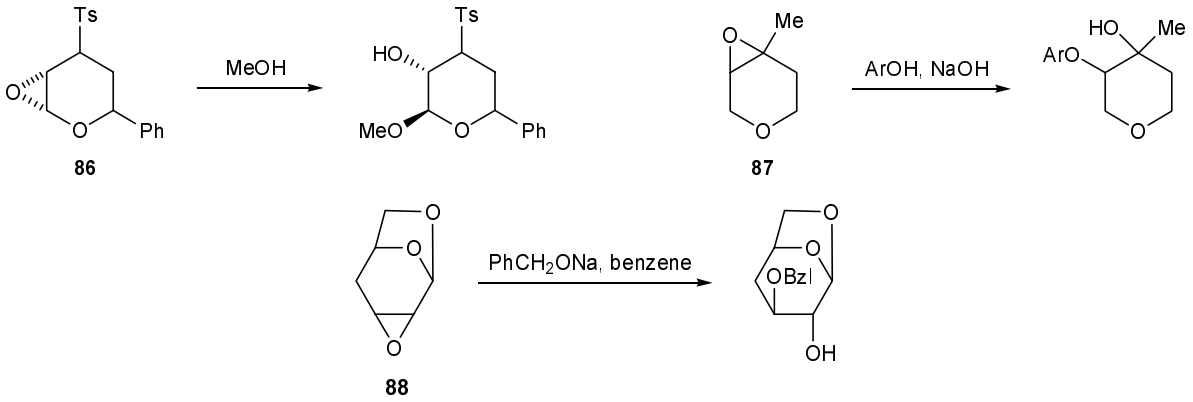


Reactions of epoxycyclohexane with β-naphthol [119] and of substituted epoxytetrahydropyrans **86–88** with various alcohols [120–123] (Scheme 32) were reported. Stereochemical behavior of epoxide **89** having a conformationally rigid bicyclic skeleton in reaction with sodium phenylmethanolate (Scheme 33) may be regarded as a proof of preferential diaxial rather than diequatorial oxirane ring opening, which was reflected in the Fürst–Plattner rule [31, 117].

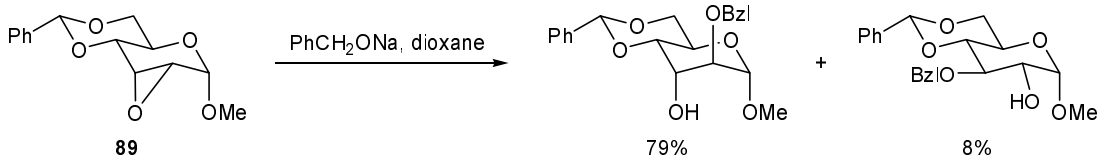
Alcoholysis of epoxides with fairly bulky reagents was reported. Kawata and Hirama [124] tried to construct kedarcidin chromophore and reacted 2-chloro-3-hydroxypyridine with epoxy compound **90**. The maximal yield of product **91** was obtained in DMF at 60°C in the presence of CeF as catalyst (Scheme 34).

Acid-catalyzed solvolysis of epoxycyclopentenone **92** involves regioselective attack by the alcohol on the

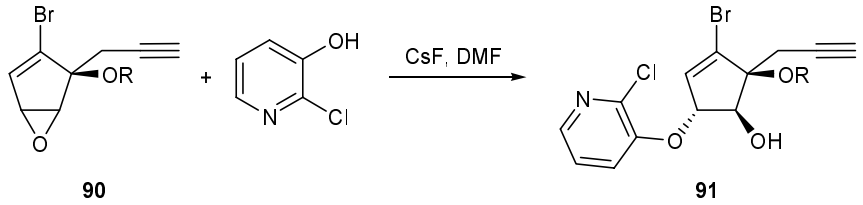
Scheme 32.



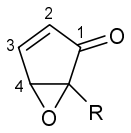
Scheme 33.



Scheme 34.



C^4 atom, and the reaction stereoselectivity depends on the substituent nature. *trans*-Opening of the oxirane ring is preferred, but participation of the substituent in the transition state could give rise to alternative stereochemical result [125]. Stereoselective reactions of 1,2-anhydro-α-furanoses **93** with various hydroxylated monosaccharide derivatives were effected in the presence of zinc chloride [126] (Scheme 35).

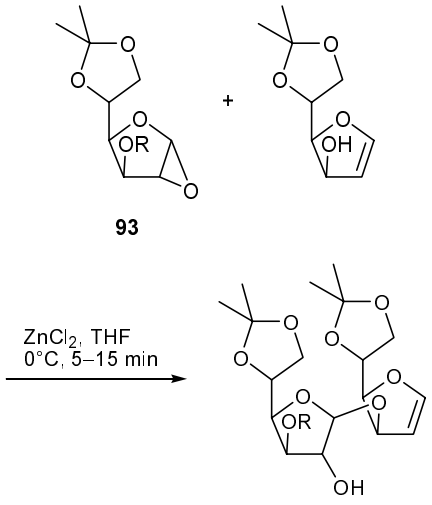


92

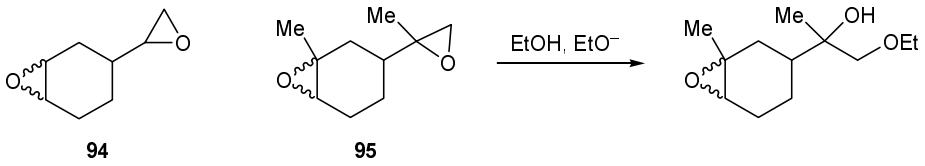
Examples of chemoselective opening of only one epoxide fragment in reactions of diepoxides with alcohols were reported. Depending on the catalyst nature, 2-(3,4-epoxycyclohexyl)oxirane (**94**) reacts with selective cleavage of one or another oxirane ring. Electrophilic catalysts favor the reaction to occur at the epoxyethyl fragment, while nucleophilic catalysts ensure opening of the fused oxirane ring. The same applies to limonene dioxide **95** [127] (Scheme 36).

Attack by ethanol on the C^1 atom of diepoxide *cis*-**95** gives rise to the only product **96** as a result of consistent action of conformational and electronic factors. By contrast, opposite effects of electronic and steric factors in the reaction with *trans* isomer *trans*-**95** are responsible for formation of two isomeric epoxides

Scheme 35.

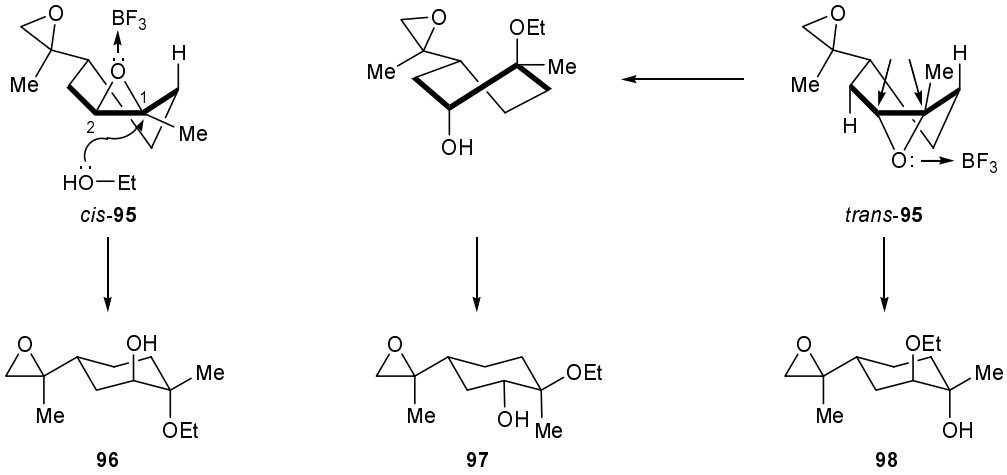


Scheme 36.



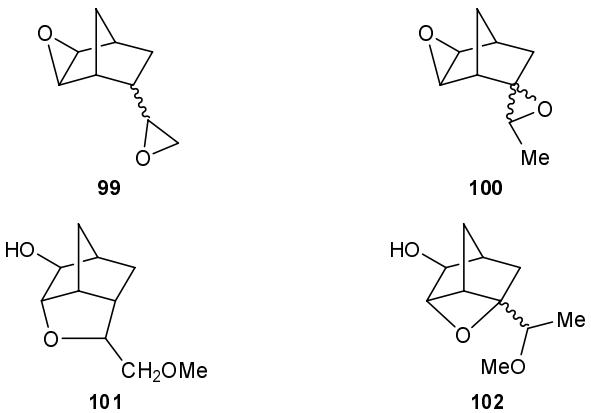
94 **95**

Scheme 37.



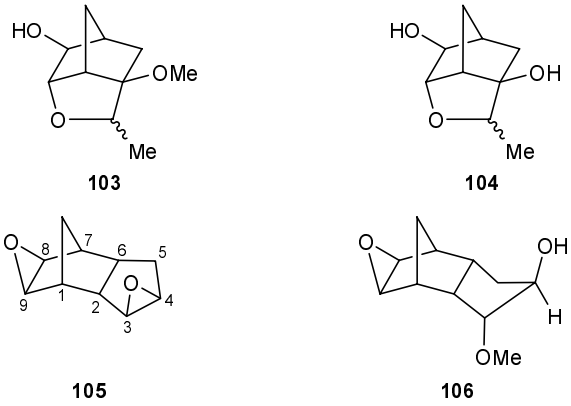
97 and **98** as the major products [127] (Scheme 37). Limonene monoepoxide with the epoxy fragment in the six-membered ring reacts similarly with ethanol in the presence of boron trifluoride [128].

Chemoselective opening of the outer epoxide fragment was observed in alkaline methanolysis of diepoxides derived from vinyl- and ethylidenenorbornenes **99** and **100** [129]; apart from primary methanolysis products, heterocyclization products **101** and **102** were formed via attack by nucleophilic alkoxide ion at the electrophilic centers of epoxynorbornane from the inner (*endo*) region of the bicyclic skeleton. The formation of oxetane fragment (**102**) does not prevent compound **100** from undergoing intramolecular cyclization. Acid-catalyzed methanolysis of diepoxides **99** and **100** follows a different pattern. The reaction rate in acid medium is higher, and both epoxy fragments are involved. From compound **99**, oxabrendane **101** and the Wagner–Meerwein rearrangement product were obtained, whereas methanolysis of diepoxide **100** afforded oxabrendanes **103** and **104** as a result of opening of the outer oxirane ring contrary and according to the Krasusky rule [130]. In both cases, heterocyclization occurs, and it may be accompanied by demethylation (compound **104**) [130].



99 **100**

101 **102**



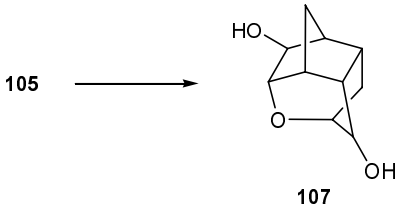
103 **104**

105 **106**

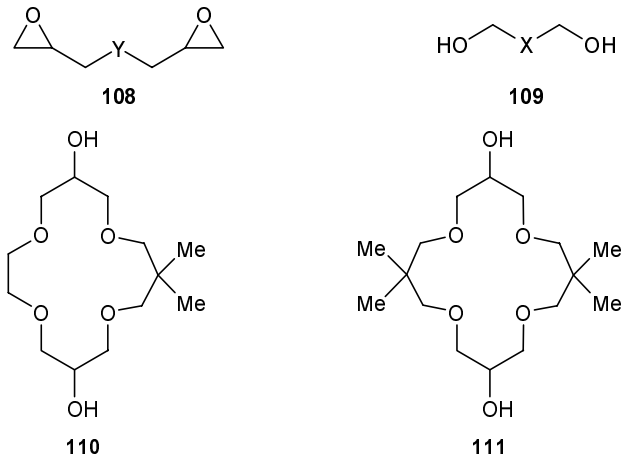
Effect of the medium was also studied with dicyclopentadiene dioxide **105** as an example [131]. In the presence of sodium methoxide, chemo-, regio-, and stereoselective opening of the epoxycyclopentane fragment gave hydroxy ether **106**. Acid-catalyzed meth-

anolysis was characterized by a higher rate, and both epoxide fragments were transformed. Here, heterocyclization occurred as a result of nucleophilic attack by the methoxy group from the *endo* region of the norbornene fragment. The structure of polycyclic diol **107** thus formed was proved by X-ray analysis [131] (Scheme 38). Semiempirical quantum-chemical study (PM3) of this reaction [132] indicated preferential attack by methoxide ion on C^4 in diepoxide **105** and leveling of the calculated energies of activation for attack by methanol on all four carbon atoms of the two oxirane fragments both for the gas-phase reaction and reaction in solution.

Scheme 38.



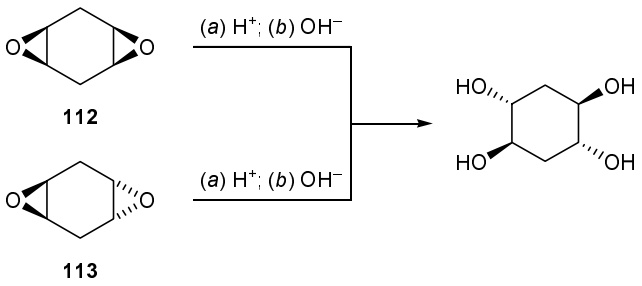
A number of polyhydroxylated macrocyclic compounds, e.g., **110** and **111**, were synthesized by condensation of diepoxides **108** [Y = O, OCH_2CH_2O, $OCH_2C(CH_3)_2CH_2O$] with difunctional nucleophiles **109** [X = $C(CH_3)_2$, CH(OBu)] [133].



6. REACTIONS OF ALICYCLIC EPOXY COMPOUNDS WITH WATER AND ORGANIC ACIDS

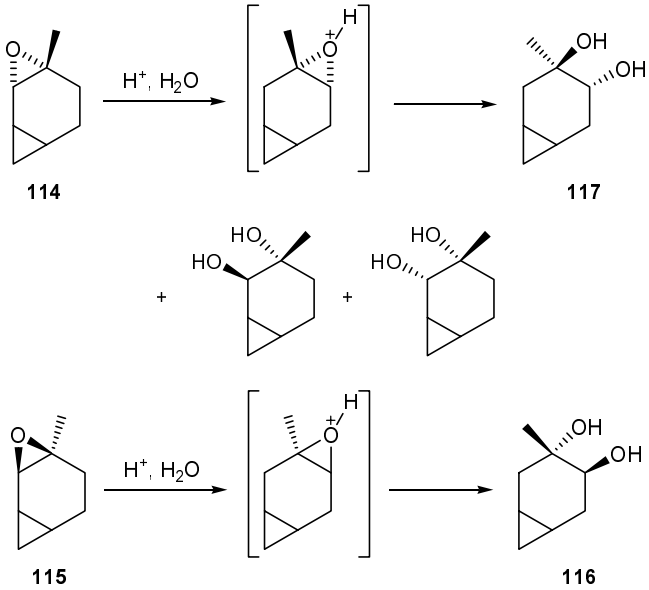
Hydrolysis of the simplest alicyclic epoxy compounds was discussed in [7, 29, 30], and no special comments are necessary; as a rule, the hydrolysis products in acid and alkaline medium are identical. The same applies to stereoisomeric diepoxides **112** and

Scheme 39.



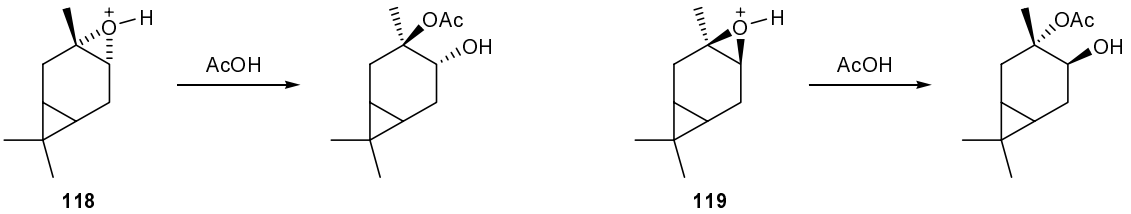
113 [134] (Scheme 39). The presence of a strained three-membered fragment at the cyclohexane ring complicates the hydrolysis pattern. Stereoisomeric 2,3-epoxynorcaranes **114** and **115** behave differently under hydrolysis conditions [135] (Scheme 40). Opening of the oxirane ring involves cleavage of the C–O bond nearest to the cyclopropane ring, for the latter is capable of stabilizing carbocationic center. Diols **116** and **117** are likely to be formed via 1,3-hydride shift, followed by 1,2(3)-migration of the epoxy ring which then undergoes cleavage at the tertiary carbon atom. The ratio of products resulting from *trans*- and *cis*-attack on *trans*-epoxide **114** is 10:1.

Scheme 40.

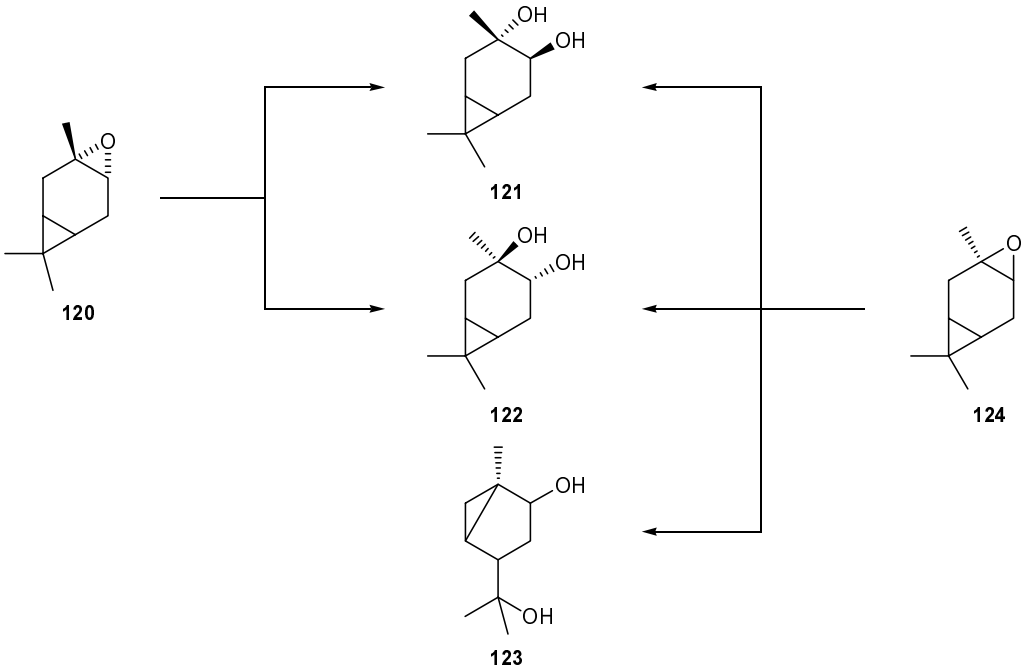


The reactions of stereoisomeric 3,4-epoxycaranes **118** and **119** with acetic acid in the presence of sodium acetate (the latter was added to minimize concomitant isomerization processes) afforded mainly *trans*-hydroxy acetates formed by cleavage of the C_{tert}–O bond [136] (Scheme 41). Treatment of *trans*-epoxide **120** with aqueous alkali gave *trans*-diols **121** and **122** at

Scheme 41.



Scheme 42.

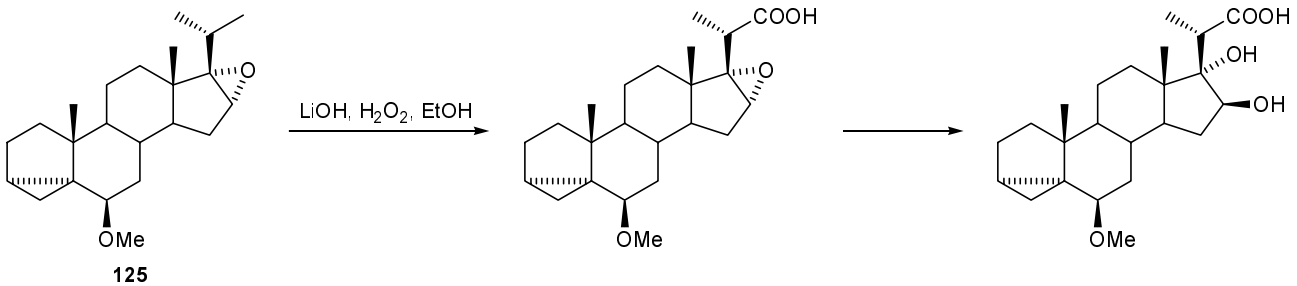


a ratio of 85:15. Analogous reaction of *cis*-epoxide **124** led to formation of of diols **121**–**123** at a ratio of 1:2:1 (Scheme 42). Presumably, base-catalyzed hydration of the epoxy ring involves both C–O bonds. In the reaction with *trans*-epoxide **120**, the attack is directed mainly at the secondary center, while *cis* isomer **124** gives rise to approximately equal amounts of products resulting from cleavage of both C–O bonds. The formation of diol **123** indicates that rearrangement of the carane skeleton into bicyclo[3.1.0]hexane can be induced by both acids and bases [137].

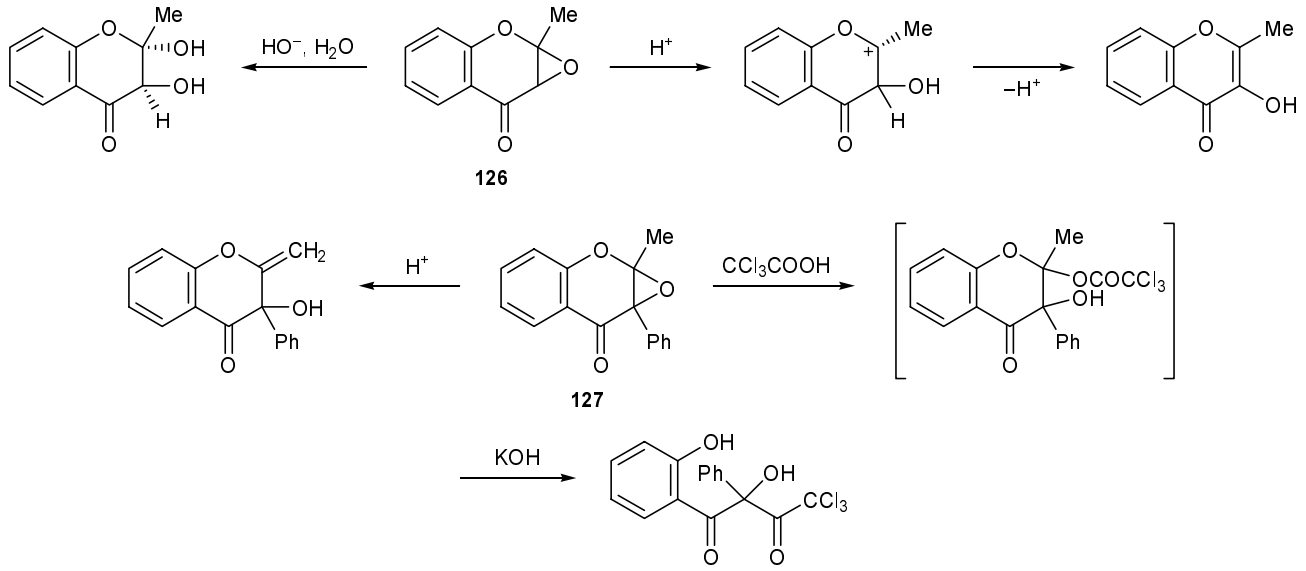
Morzycki *et al*. [25] studied reactions of 16α,17α-epoxy steroid **125** with a view to obtain new potential antitumor drugs (Scheme 43). The hydrolysis and trichloroacetolysis of epoxychromones (which are structurally related to naturally occurring epoxy compounds) was reported in [138]. Compounds **126** and **127** underwent different transformations in acid medium, while conventional products were obtained from both these under basic conditions.

Barili *et al*. [139] synthesized stereoisomeric isobutyl 3,4-anhydro-2,6-dideoxy-DL-hexopyranosides

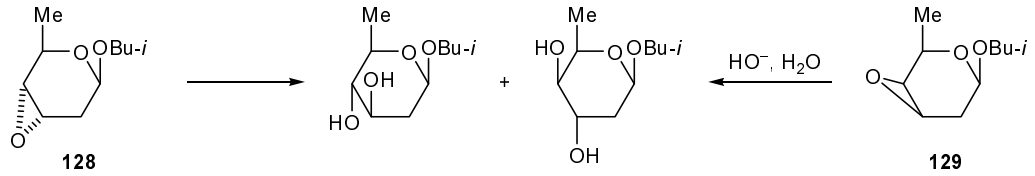
Scheme 43.



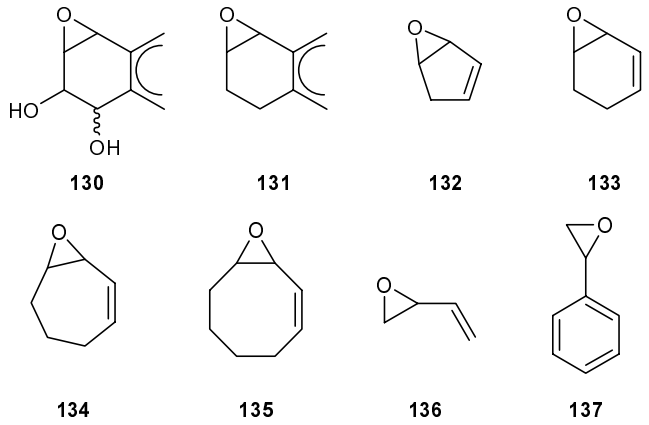
Scheme 44.



Scheme 45.

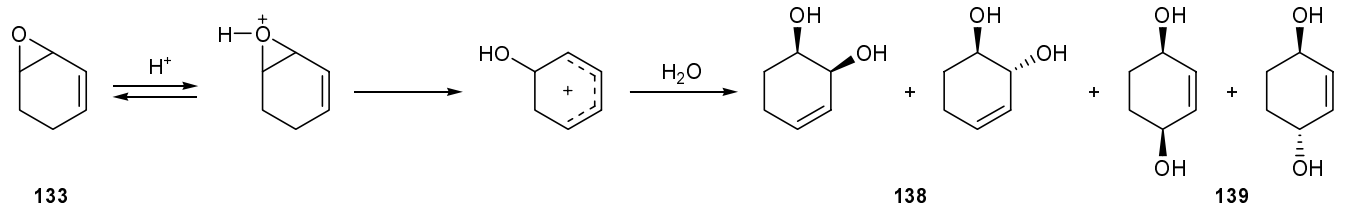


128 and **129** and examined how their stereochemical structure affects the regioselectivity of their transformations under conditions of alkaline hydrolysis. The hydrolysis of *lyxo*-epoxide **129** was regio- and stereoselective, while *ribo*-epoxide **128** gave rise to a mixture of *xylo*- and *arabino*-diastereoisomers (Scheme 45). Enzymatic hydrolysis of **129** afforded the same diol in quantitative yield. Taking advantage of the higher rate of hydrolysis of the L-enantiomers, optically active diols were isolated. The process was monitored by NMR spectroscopy using a chiral shift reagent [139].



Epoxides **130–137** were used as substrates in studies on the structure–reactivity relations holding in their hydrolysis [140, 141]. An ethylene group conjugated to epoxide fragment acts in a way similar to an aromatic system. The hydrolysis of epoxycyclopentene **132** at pH ≈ 7 is characterized by a half-conversion period of 2.2 min, while structurally related epoxycyclohexene **133** is even more reactive [140]. Similarity of 1,2-epoxides derived from cycloalka-1,3-dienes to practically important epoxy derivatives of polycyclic aromatic hydrocarbons stimulates thorough studies on their structure, properties, and chemical behavior. Ross *et al.* [140] examined the rates of hydrolysis of 3,4-epoxycycloalkenes as a function of pH. The product structure and kinetic data led the authors to postulate S_N1 (A1) mechanism involving intermediate formation of allyl-type cation. The hydrolysis of epoxy compound **133** with potassium hydroxide gave diol **138** as the only product. The hydrolysis of **133** in the presence of sodium perchlorate (pH 5–9) and potassium chloride (pH 2–12) was stereoselective, and *trans*-diols **138** and **139** were formed in more than 80% yield (Scheme 46). With rise in pH, the fraction of diol **138** increased from 50–60 to 99%, while the fraction of **139** fell down from 30–40 to 1%. The

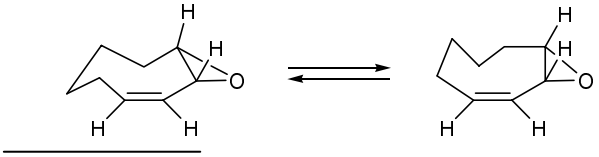
Scheme 46.



observed stereoselectivity was rationalized in terms of specific stereochemical properties of cyclohexenyl cation [140].

Compounds **132** and **134** gave rise to comparable amounts of the corresponding *cis*- and *trans*-diols. Epoxide **135** turned out to be less reactive than **132**–**134** by about three orders of magnitude, and it did not undergo spontaneous hydrolysis. The low reactivity of **135** was attributed to considerably enhanced angular strains and/or nonbonding interactions typical of medium-size rings in the transition state; the latter is likely to have a structure similar to cyclooctenyl cation, as follows from the product composition. Presumably, epoxide **135** reacts as two equilibrium conformers (*twist–boat–chair* and *twist–boat*) having approximately equal energies [140] (Scheme 47).

Scheme 47.

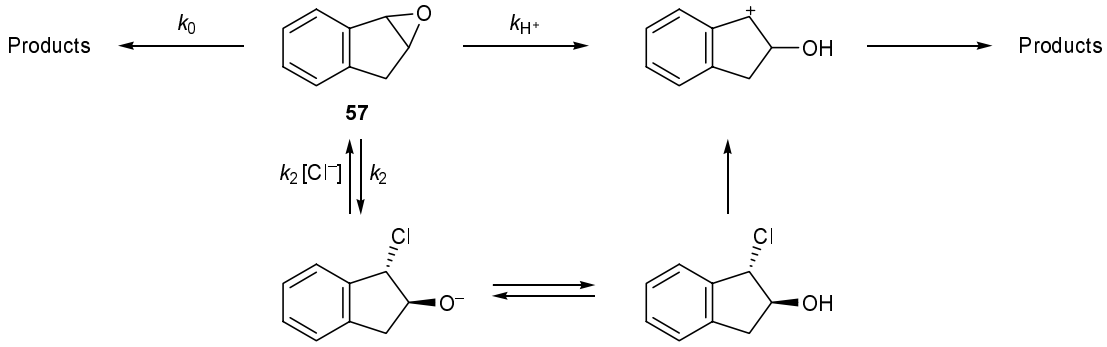


A specific effect of chloride ions was revealed in the hydrolysis of epoxides **132**, **133**, and **137**; analogous effect was reported previously for hydrolysis of epoxyindan [141]. Nucleophilic addition of chloride ion to neutral epoxide **57** gives an intermediate which exists in equilibrium with the protonated species. This reaction occurred at pH 7–8.5; at lower pH values, acid-catalyzed opening of the epoxy ring was observed, while the substrate reacted with the solvent (k_0) at higher pH (Scheme 48).

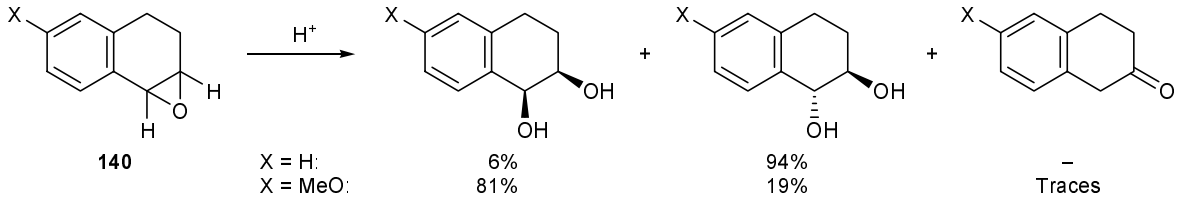
Both acid-catalyzed and spontaneous hydrolysis of epoxytetrahydronaphthalene **140** (which can be regarded as analog of epoxycyclohexene **133** containing fused benzene ring instead of the olefinic fragment) resulted in predominant formation of the corresponding *trans*-diol [142, 143] (Scheme 49).

The stereoselectivity was changed toward formation of 81% of the *cis*-diol by introducing an electron-donor methoxy group which enhanced stabilizing effect of the benzene ring via reduction of positive charge in the benzylic position. Increased stability of the cation formed by protonation of methoxy-substituted epoxide favors its conformational isomerization

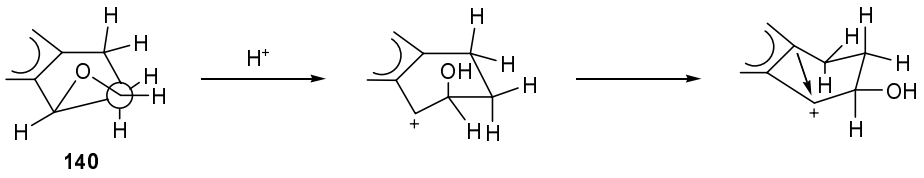
Scheme 48.



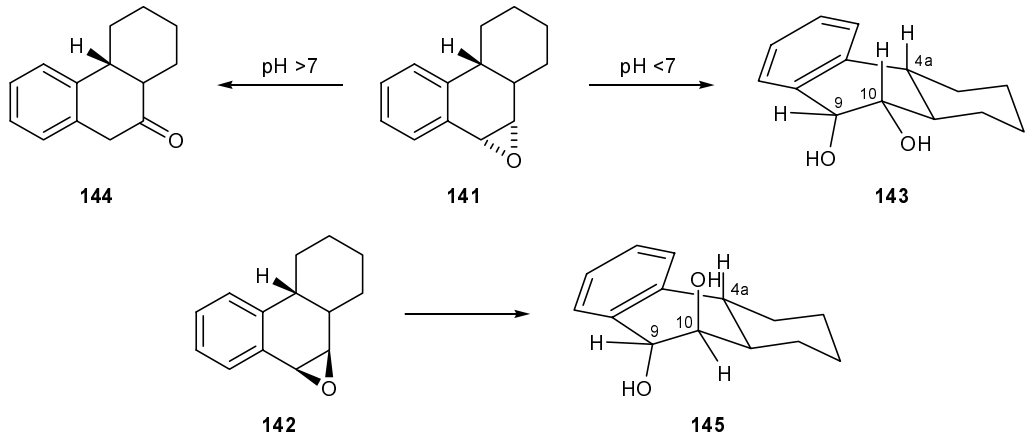
Scheme 49.



Scheme 50.



Scheme 51.

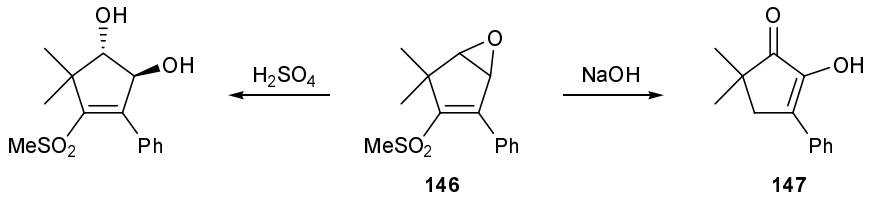


thus altering the direction of nucleophilic attack (Scheme 50).

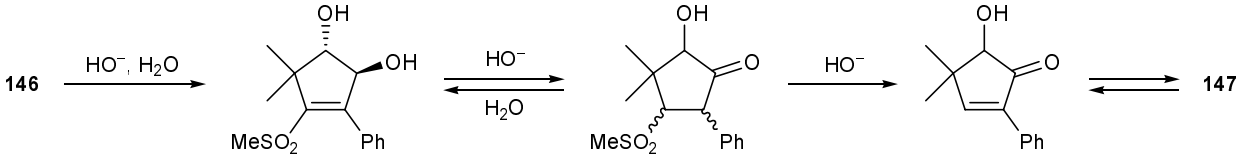
Sayer *et al*. [144] synthesized diastereoisomeric 9,10-epoxides **141** and **142** derived from *trans*-1,2,3,4,4a,10a-hexahydrophenanthrene as structural analogs of compounds in which the epoxy group is a part of a *bay region* of the hydrocarbon. Inspection of molecular models indicated that one of these epoxides (**141**) has the benzylic C–O bond of the epoxide ring aligned nearly parallel to the π orbitals of the aromatic ring and that the C–O bond in the other diastereoisomer (**142**) is not aligned in such a way. The rate constants of acid hydrolysis (k_{H^+}) for both diastereoisomers are similar, whereas neutral hydrolysis of **141** is ~40 times faster than that of **142**. Upon solvolysis, nonaligned diastereoisomer **142** yields exclusively *trans*-diol **145**, while aligned isomer **141** yields predominantly *cis*-diol **143** (75%) under acidic conditions and ketone rearrangement product **144** (~85%) under neutral conditions (Scheme 51).

The behavior of chemically labile epoxycyclopentene derivatives essentially depends on the reaction medium [145] (Scheme 52). Presumably, epoxide **146** in alkaline medium undergoes rearrangement according to Scheme 53 [145]. Triacetoxyborane was reported as a novel reagent for epoxide ring opening with formation of acetoxy derivatives **148** and **149** [146] (Scheme 54). More complex reaction mixtures were

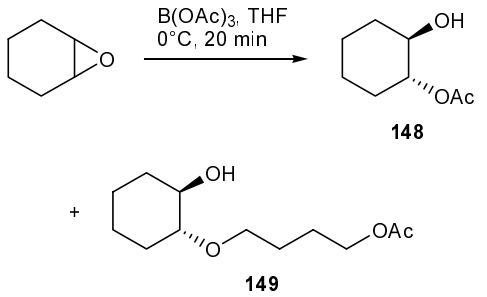
Scheme 52.



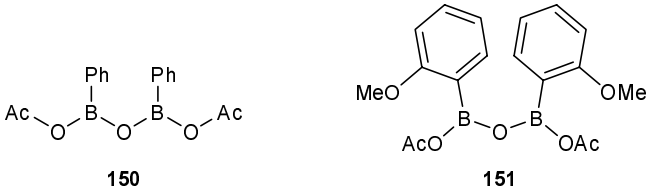
Scheme 53.



Scheme 54.

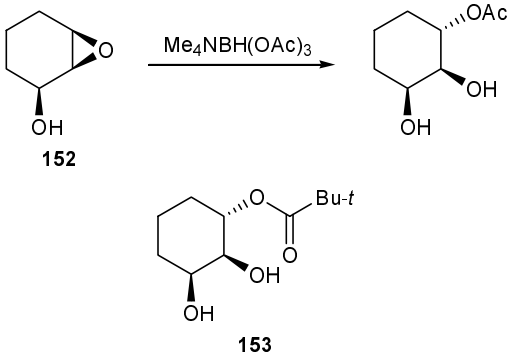


obtained with the use of other boron compounds, e.g., like **150** and **151**.

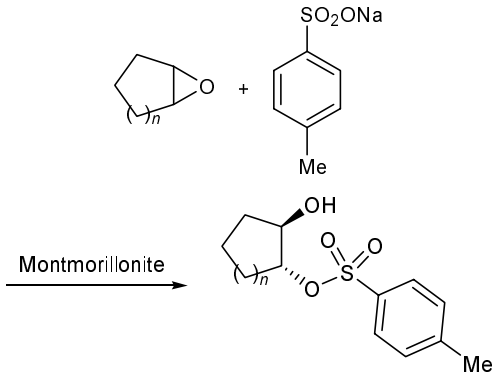


Tetramethylammonium triacetoxohydridoborate ensured high yield and regioselectivity in reactions of epoxy alcohols, e.g., of 2,3-epoxycyclohexanol (**152**) [147] (Scheme 55). In the presence of pivalic acid, the major product was ester **153**.

Scheme 55.

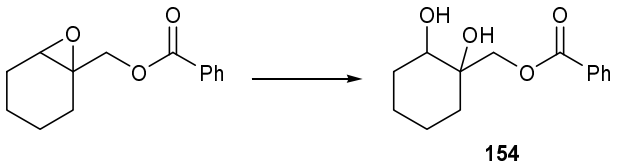


Scheme 56.



Dupuy *et al*. [148] studied reactions of epoxides with sodium *p*-toluenesulfonate catalyzed by montmorillonite (Scheme 56). Dihydroxy esters like **154** were obtained from the corresponding epoxy esters by the action of molecular oxygen in the presence of Ni(II) catalyst [149] (Scheme 57).

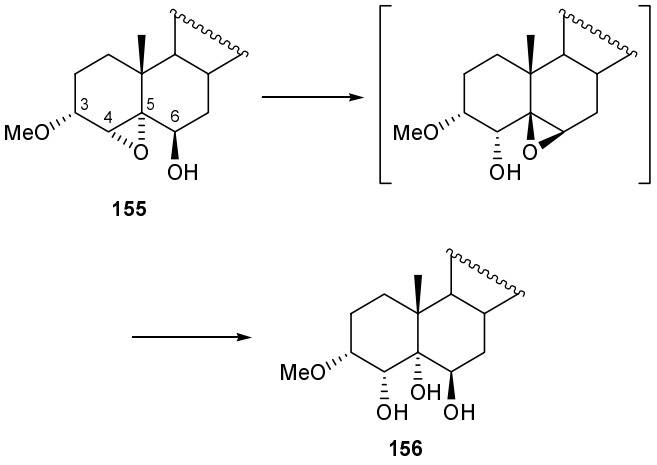
Scheme 57.



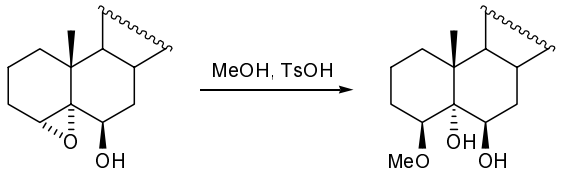
7. UNUSUAL REACTIONS OF EPOXY COMPOUNDS WITH OXYGEN-CENTERED NUCLEOPHILES

This section describes some examples of unusual behavior of epoxides in acid solution. Morrison and Wilkinson [150] reported on acidolysis of steroid 6β-hydroxy-4α,5α-epoxides **155** by the action of perchloric, acetic, and formic acids. If attack on C^4 by an external nucleophile is inhibited due to inductive effect of the 3-methoxy group, migration of the epoxy group occurs via intramolecular attack on C^5 by the neighboring hydroxy group. The final product is formed as a result of either rearrangement or diaxial cleavage of isomeric intermediate epoxide. Thus product **156** corresponds to overall *cis*-opening of the original oxirane ring (Scheme 58). Acid-catalyzed methanolysis of epoxy compound **157** having no methoxy group on C^3 gives 4-methoxy diol as a result of *trans*-diaxial cleavage of the oxirane ring by external nucleophile (Scheme 59).

Scheme 58.

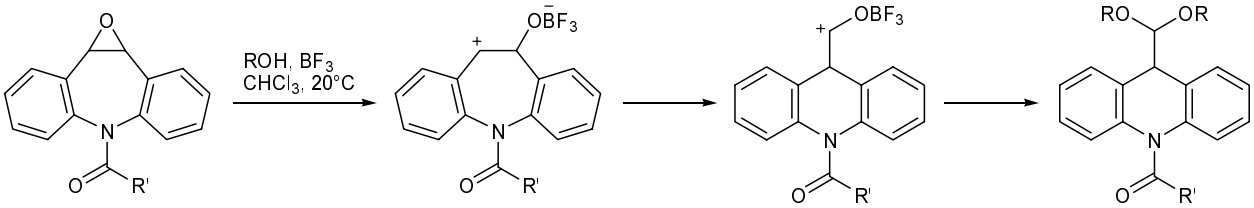


Scheme 59.



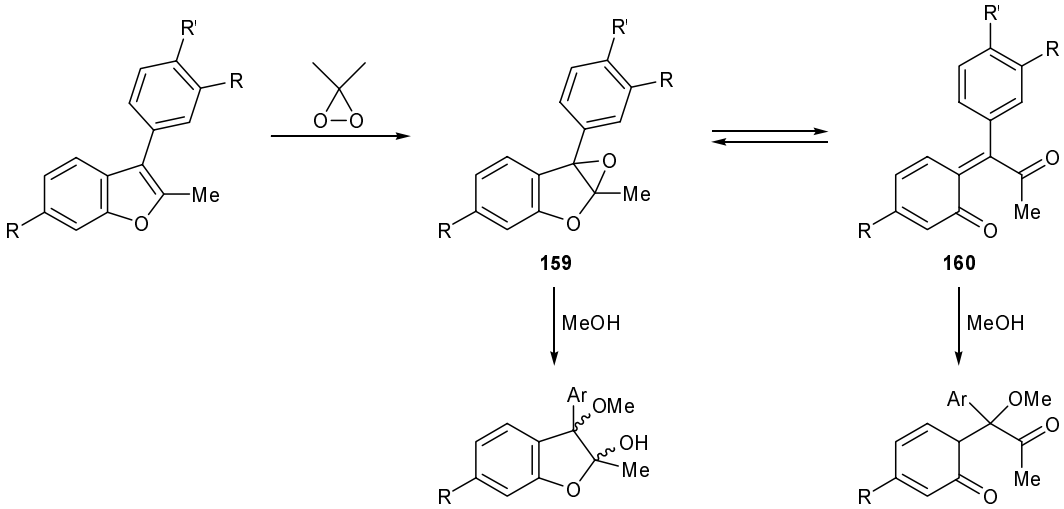
157

Scheme 60.

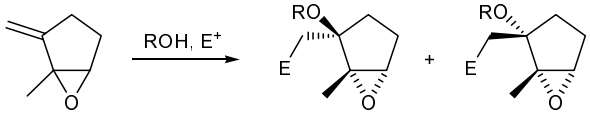


158

Scheme 61.

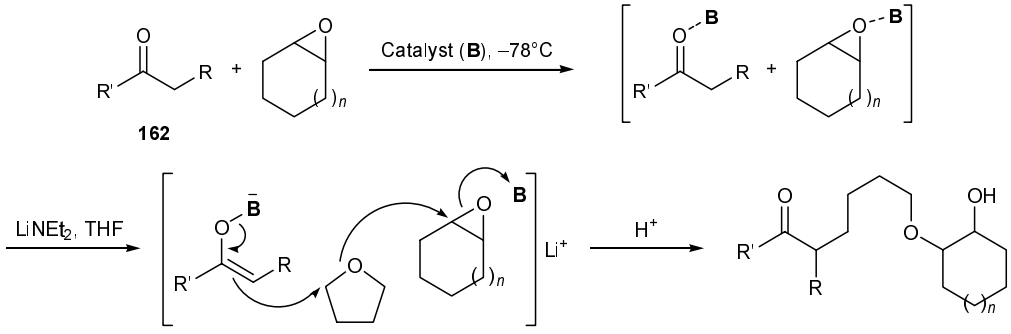


Scheme 62.



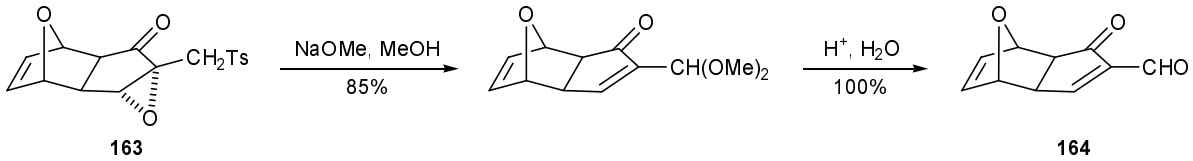
161

Scheme 63.



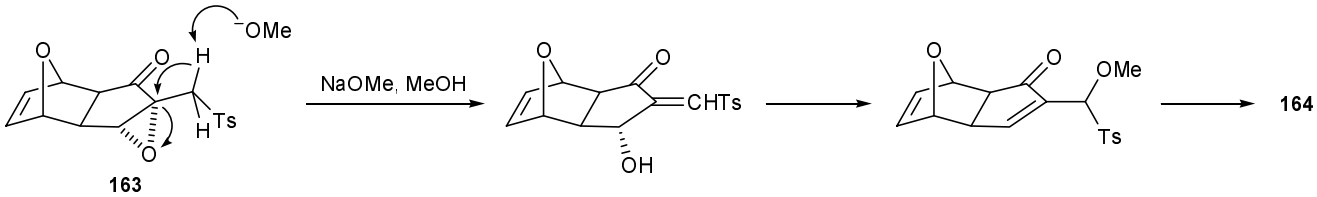
162

Scheme 64.



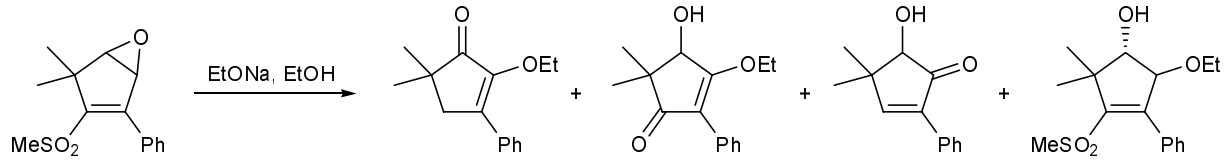
163 164

Scheme 65.



163

Scheme 66.



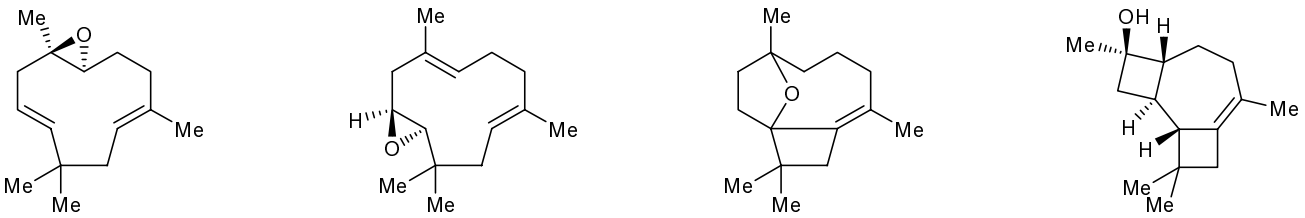
146 165 166

A certain interaction between positions *4*, *5*, and *6* in the series of epoxy steroids was observed in other transformations. It is known that two isomeric compounds, 4β-acetoxyandrost-5-en-17-one and 6β-acetoxyandrost-4-en-17-one, react with *m*-chloroperoxybenzoic acid to afford in each case a mixture of 4β-acetoxy-5α,6α-epoxy- and 6β-acetoxy-4α,5α-epoxyandrostan-17-ones. This was interpreted in terms of a symmetrical "acetoxylinium" (1,3-dioxan-2-ylium) ion and a degree of charge separation in the transition state for epoxidation [151], i.e., favorable mutual arrangement of the fragments attached to the C^4, C^5, and C^6 atoms.

Alcoholysis of 5-acyl-10,11-epoxy-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepines **158** in the presence of $BF_3 \cdot Et_2O$ was accompanied by isomerization and azepine ring contraction [152] (Scheme 60). Valence isomerization of epoxybenzofurans **159** into quinone analogs **160** was observed [153] (Scheme 61). Reactions of alcohols with epoxytetrahydrofuran **161** in the presence of electrophilic catalysts did not involve the oxirane ring [154] (Scheme 62). Saito *et al*. [155] reported on an unusual ether bond formation in the three-component reaction of ketone **162**, cyclic ether (tetrahydrofuran), and epoxycycloalkane. Here, the ether bond was formed by the action of tris(2,6-diphenylphenoxy)aluminum (**B**) in the presence of lithium diethylamide **C** which favors enolization of ketones (Scheme 63).

Carrying out the reaction in alkaline medium does not ensure normal way of oxirane ring opening. For example, 4,5-epoxy-4-tosylmethyl-10-oxatricyclo-[5.2.1.$0^{2,6}$]dec-8-en-3-one (**163**) smoothly reacts with sodium methoxide in methanol to give aldehyde **164** (Scheme 64). The reaction involves initial proton abstraction from C^{11} and subsequent opening of the epoxide ring [156] (Scheme 65).

Treatment of highly reactive epoxy compound **146** with sodium ethoxide in ethanol led to formation of a mixture of products, the fraction of expected compound **166** being small [145] (Scheme 66). A series of hydrolysis products were obtained at pH 7 from epoxy



167 168 169 170

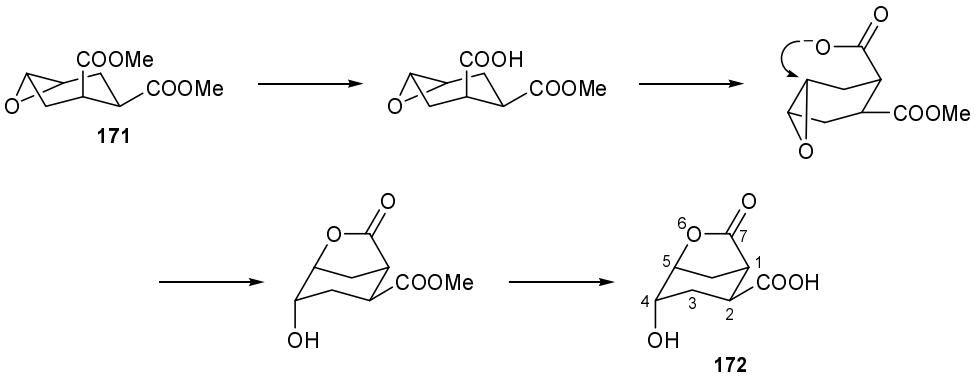
derivatives of humulene (compounds **167** and **168**) [157]. Compounds **169** and **170** were isolated by HPLC; they were likely to be formed as a result of molecular rearrangements of epoxy compound **167**.

An interesting pattern was observed with stereoisomeric dimethyl *cis*- and *trans*-4,5-epoxycyclohexane-*cis*-1,2-dicarboxylates in the presence of pig liver esterase which is known to favor hydrolysis of methoxycarbonyl group to carboxy [158]. The *cis* isomer turned out to be stable under these conditions, while *trans* isomer **171** underwent hydrolysis, followed by intramolecular cyclization. As a result, (1*R*,2*S*,4*S*,5*S*)-4-hydroxy-7-oxo-6-oxabicyclo[3.2.1]octane-2-carboxylic acid (**172**) was isolated (Scheme 67). Stereoselective opening of the oxirane ring in epoxycyclopentane **173** on treatment with aqueous sodium hydroxide at 75°C involved intermediate heterocyclization [133] (Scheme 68). Analogous participation of an amide carbonyl group was reported by Katagari *et al*. [159] for the hydrolysis of epoxy compound **173** in the presence of boron trifluoride. Classical isomerization of epoxides **174** and **175** into carbonyl-containing systems occurred under acidic conditions [160, 161] (Scheme 69). Unusual products were obtained by acid hydrolysis of epoxytricyclo-[4.2.2.0^{2,5}]decane derivative **176** in a mixture of acetic acid and acetic anhydride in the presence of lithium perchlorate [162] (Scheme 70). Although addition of perchloric acid salts is known to strongly influence the composition of epoxide ring opening products, the authors were the first to demonstrate the possibility for formation of perchloric acid esters by opening of oxirane ring. These data indicated that even such a weak nucleophile as perchlorate ion is capable of competing with strong nucleophiles (such as water and acetate ion) for attack on epoxide ring.

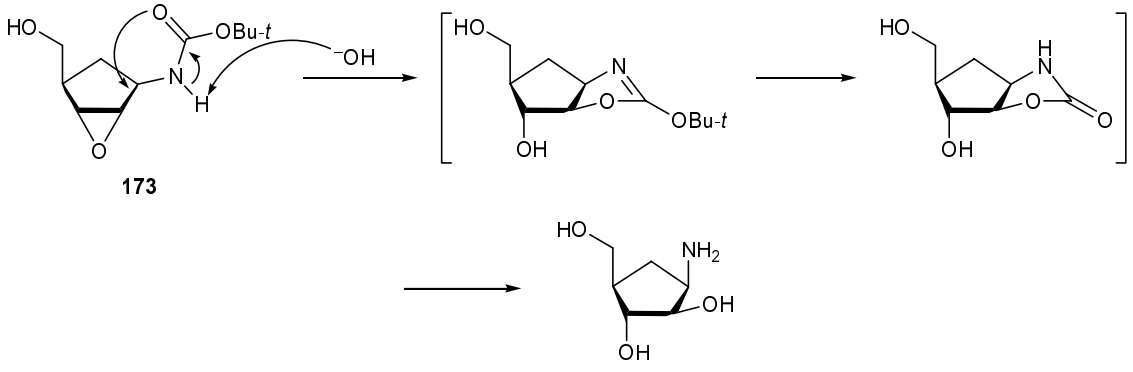
In view of modern concepts of participation of epoxides in metabolism of various classes of unsaturated compounds (both endogenous and xenobiotics) in living organisms, the problem of epoxide ring opening with different nucleophiles has become very important. The nature of nucleophile involved in a reaction determines the ratio between detoxicating effects (transformation into nonhazardous metabolites and their removal from organism) and hazardous processes, such as teratogenic, carcinogenic, and embryotoxic actions [163].

Nucleophilic properties of nucleofugal anions were proved by studying reactions of oxirane, 1,2-epoxypropane, and epoxycyclohexane with protic acids

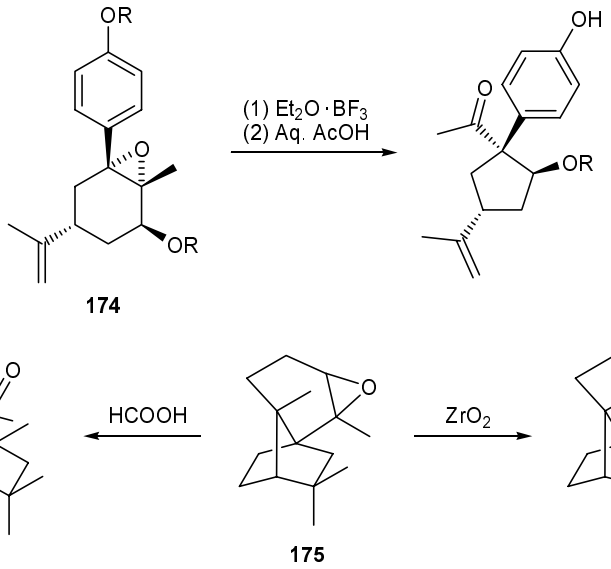
Scheme 67.



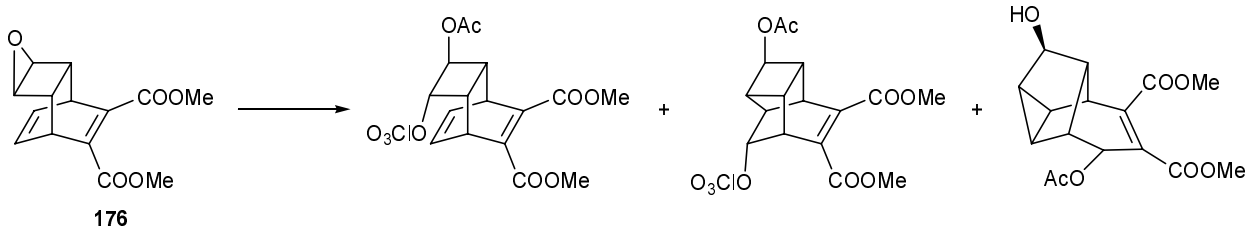
Scheme 68.



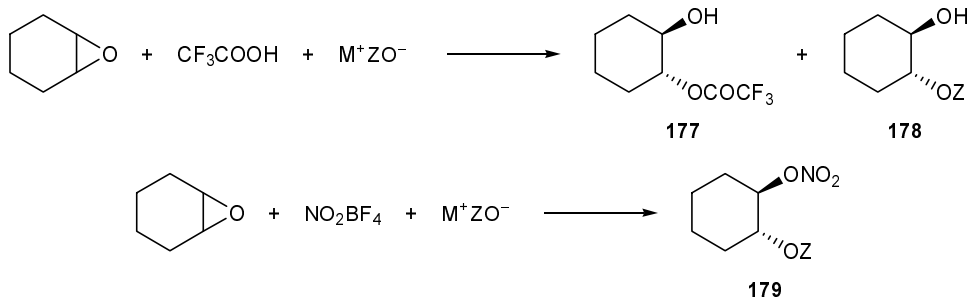
Scheme 69.



Scheme 70.



Scheme 71.



(acetic and trifluoroacetic) in the presence of a source of nucleophilic anions (lithium or tetrabutylammonium salts of perchloric acid or various sulfonic acids) [163]. Apart from 2-hydroxyalkyl carboxylates **177**, these reactions afforded considerable amounts of 2-hydroxyalkyl perchlorates or sulfonates **178** (Z = ClO_3, Ts, Ms; yield 35–70%). The yield of nitroxy derivatives **179** attained 90% in reactions with nitronium tetrafluoroborate (Scheme 71). The results obtained by Zefirov and co-workers [163] are quite consistent with the classical concepts of the mechanism of epoxide ring opening [29–31]. The presence of a fairly large positive charge on the carbon atom in "loose" transition state is responsible for the possibility for epoxides to react with nucleofugal anions, which leads to formation of perchloric and sulfonic acid esters.

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